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Council on Pharmacy & Chemistry

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PREFACE

This volume—the Annual Reprint of the Reports of the Council on Pharmacy and Chemistry of the American Medical Association—contains the reports of the Council that have been adopted and authorized for publication during 1923. It includes reports of the Council previously published in THE JOURNAL, along with such editorial comments as have accompanied them. In addition, the volume contains reports of the Council which, because of their lesser importance, were not published in THE JOURNAL, and which as a matter of record are included here. That the Council's official reports may be made available to physicians, chemists, pharmacologists and others interested in medicine, the Council authorized publication of this volume.

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Report of the Council on Pharmacy and Chemistry

The Council has authorized publication of the following statement. W. A. PUCKNER, Secretary.

Acetylsalicylic acid-L. & F. (Lehn & Fink, New York) was accepted as a brand of acetylsalicylic acid-N. N. R. in 1917. As the period for which the product stood accepted expired with the close of 1923, the Council requested Lehn & Fink to send the labels and advertising now used for the product. The firm in reply informed the Council that in consideration of the ruling of Judge Hand the name acetylsalicylic acid-L. & F. had been changed to aspirin on all packages containing fifty tablets or less. Judge Hand of the U. S. District Court, Southern District of New York, in the case of The Bayer Company against the United Drug Company, has ruled that acetylsalicylic acid must be sold under its descriptive name to druggists and physicians, but may be sold to the public as "aspirin," the name under which the drug was introduced. It thus appeared that acetylsalicylic acid-L. & F. was ineligible for continued inclusion in New and Nonofficial Remedies for the reason that (as aspirin) it was being sold to the public.

That Lehn & Fink market their aspirin for indiscriminate use by the public is shown by the following, which appears on a "vest pocket" size of the firm's aspirin tablets: "When to Use. For colds, acute rheumatism, headache, neuralgia or other pains of nervous origin. Also for the relief of gout, sciatica, tonsilitis, influenza." Enclosed with the vest pocket package is a slip which advertises the firm's proprietary brand of liquid petrolatum to the public. It reads: "The Modern Remedy for Constipation. Lehn & Fink's Regulol. Pure Russian Mineral Oil. The Perfect Lubricant."

The Council has rescinded its acceptance of acetylsalicylic acid-L. & F. and directed its omission from New and Nonofficial Remedies because, as aspirin, it is advertised to the public for indiscriminate self-medication and because it is used as a means of advertising an unacceptable preparation, "Regulol."

ADRENAL COMP. VAGINAL SUPPOSITORIES-MULFORD AND OINTMENT CARGENTOS ICHTHYOL OMITTED FROM N. N. R.

Report of the Council on Pharmacy and Chemistry

The Council has authorized publication of the following announcement.

W. A. PUCKNER, Secretary.

Adrenal Comp. Vaginal Suppositories-Mulford and Ointment Cargentos and Ichthyol contain Ichthyol as one of their ingredients. The Council has omitted Ichthyol from New and Nonofficial Remedies, and as it does not recognize products which contain a nonofficial article not in New and Nonofficial Remedies, it has been obliged to rescind the acceptance of Adrenal Comp. Vaginal Suppositories-Mulford and Ointment Cargentos and Ichthyol.

Accordingly, these preparations are omitted from New and Nonofficial Remedies.

ALBARGIN NOT ACCEPTED FOR N. N. R.

Report of the Council on Pharmacy and Chemistry

From the Journal A. M. A., Aug. 25, 1923, p. 677

The Council has authorized publication of the following report. It declares Albargin inadmissible to N. N. R. because (1) it is an unessential modification of silver nitrate and (2) the therapeutic claims are unwarranted.

W. A. PUCKNER, Secretary.

Albargin is a product of Farbwerke, vorm. Meister, Lucius and Bruening, Hoechst. a. M., Germany. The claim is made that it is a compound of silver nitrate with gelatose, containing 15 per cent. of silver. Albargin was formerly described in New and Nonofficial Remedies. In 1919, after Sollmann *(Jour. Am. Pharmaceutical Assn.,* Vol. 7, p. 77) had shown that, contrary to the claims advanced for it, Albargin contained silver ions, precipitated chlorids and albumin and produced irritation, the Metz Laboratories (the American distributors) were informed of these facts. They were advised that the continuance of Albargin in New and Nonofficial Remedies was conditioned on a thorough revision of the claims. The Metz Laboratories withdrew the advertising then in use and agreed to revise the claims when further advertising was issued. On this agreement Albargin was retained. Subsequently, however, it was omitted because it was off the market.

Albargin being again available, the Metz Laboratories requested its reacceptance for New and Nonofficial Remedies. They submitted an advertising leaflet in which were reiterated the claims for non-irritation and absence of pain to which objection had been made in 1919, omitting only the claim for non-precipitation of albumin and chlorids.

For example, the present advertising contains such claims as:

"Albargin combines the advantages of albumin compounds of silver and of silver nitrate."

"Dialyses through animal membranes, thus possessing an invaluable therapeutic advantage."

"Because of its dialysing properties, Albargin possesses far greater power than other albumin compounds of silver to penetrate living membranes and tissues."

". . . Produces neither irritation nor pain."

The Metz Laboratories were asked for the details of the experiments which formed the basis for the claim that Albargin dialyzes through animal membranes. Attention also was called to the fact that the present advertising contained claims that had been objected to in 1919, and that experiments had shown that Albargin contained about one-fifth as much ionic silver as does silver nitrate.

As evidence that Albargin dialyzes through animal membranes, the firm sent references to the literature, including a report by P. G. Unna and Golodetz (*Dermatol. Wochenschrift*, 1917, No. 20), and of C. Cronquist, Malmoe (*Therap. Monatschr.* April, 1909). A number of abstracts and reprints of clinical papers were also submitted.

An examination of specimens of Albargin shows that its antiseptic activity, determined by a modified Dreser yeast method, is exactly the same as that of a silver nitrate solution of equal silver content, the silver content by this biologic method being 14.55 per cent. An independent chemical determination made in the A. M. A. Chemical Laboratory on the same specimen demonstrated that it contained 14.4 per cent. of total silver. This correspondence shows that all of the silver in Albargin is in ionic form and none in the colloidal form. In other words, the silver of Albargin is not combined with gelatose but is in the same condition as the silver of silver nitrate. That the silver is in ionic form is confirmed by the dialysis of Albargin according to the papers of P. G. Unna and Golodetz and of C. Cronquist, cited by the Metz Laboratories as evidence. The silver of Albargin dialyses readily, which would not be the case if it were combined with the gelatose. It is the silver nitrate that dialyses and not the "Albargin."

There remained the theoretical possibility that the gelatose might mitigate the irritant action of the silver nitrate by acting as an indifferent demulcent. To determine this point, a 0.5 per cent. solution of Albargin was compared with a 0.1 per cent. solution of silver nitrate. The two solutions had approximately the same silver content. The irritant action was tested on the nose and mouth by two persons who had experience in such comparison. Neither could detect a notable difference.

The clinical abstracts and papers that were submitted agreed in affirming the efficiency of Albargin in the treatment of gonorrheal infections, but did not claim that it is more efficient than silver nitrate solutions of equal silver content. In these it is claimed that Albargin is not seriously irritant in therapeutic concentrations, but in none is it stated that the actual comparisons have been made with silver nitrate solutions of equal silver content. They contain the claim—evidently erroneous—that Albargin does not precipitate proteid, but without having tried the experiment.

The evidence forces the conclusion that solutions of Albargin act in every way like solutions of silver nitrate of the same silver content and that the action of Albargin is due solely to the silver nitrate it contains. As the gelatose serves no useful purpose, its presence in Albargin is unscientific.

In view of these facts the Council declares Albargin inadmissible to New and Nonofficial Remedies because (1) it is an unessential modification of silver nitrate and (2) the therapeutic claims are unwarranted.

APIOL OMITTED FROM N. N. R.

Report of the Council on Pharmacy and Chemistry

The Council has adopted the following report announcing the omission of Apiol from New and Nonofficial Remedies.

W. A. PUCKNER, Secretary.

Whereas the U. S. Pharmacopeia recognizes oleoresin of parsley fruit or liquid apiol, New and Nonofficial Remedies describes the pure principle apiol or parsley camphor.

Preparations of parsley fruit have been used for many years for their asserted antiperiodic and emmenagogue effects, particularly in the form of proprietary preparations. During this time, no good evidence has become available to indicate that they are useful therapeutic agents. On the other hand, D. I. Macht (The Action of So-called Emmenagogue Oils on the Isolated Uterine Strip, *Jour. Exper. Pharmacol.*, 1913,

Vol. 4, p. 547; THE JOURNAL A. M. A., Nov 8, 1913, p. 1725) studied the action of so-called emmenagogue oils, including apiol, and found that these preparations had no specific or directly stimulating action on the uterine muscle, but on the contrary they inhibited the contractions of the uterus and even paralyzed it. There is no acceptable evidence for the value of apiol as a therapeutic agent.

In consideration of the fact that during the many years of use no satisfactory evidence for the therapeutic usefulness of parsley seed preparations has become available, the Council directed the omission of apiol from New and Nonofficial Remedies. As a matter of record the description of apiol which appeared in New and Nonofficial Remedies, 1922, is appended.

APIOL. — Apiolum Crystallisatum. — Parsley Camphor. — $CH_2 : CH.CH_2C_6H(OCH_3)_2 : O_2 : CH_2CH$. — 2,5-dimethoxy-3,4-methendioxy-1^2propenylbenzene, derived from 2,3,4,5-tetrahydroxy-1-propen (1^2) yl-benzene, $C_6H(OH)_4(CH_2CH : CH_2)$.

Actions and Uses.—Apiol is said to produce cerebral excitation similar to that induced by coffee and, in larger doses, a species of intoxication, with vertigo, ringing in the ears and severe frontal headache.

Apiol has been used as an antiperiodic, but is regarded as of inferior rank for this purpose. It has also been recommended in the treatment of amenorrhea.

Dosage.—From 0.13 to 0.3 Gm. (2 to 5 grains) in capsules, as an emmenagogue; from 0.3 to 1 Gm. (5 to 15 grains) as an antipyretic.

Apiol may be obtained by extracting the oleoresin (oleoresin of parsley seed) with ether and subsequent purification. It may also be obtained by submitting parsley seed to steam distillation, cooling the volatile oil and collecting and purifying the crystals which separate.

Apiol crystallizes in long needles, having a faint odor of parsley, melting at 30 C. and boiling at 294 C. It is insoluble in water, but readily soluble in alcohol and ether. Combined with strong sulphuric acid, it forms a blood-red solution. Apiol is not affected by aqueous solutions of potassium or sodium hydroxid, but by alcoholic solutions of potassium or sodium hydroxide it is gradually converted to isoapiol, which melts at 56 C.

BENETOL

Report of the Council on Pharmacy and Chemistry

The Council has authorized publication of the following report.

W. A. PUCKNER, Secretary.

Benetol—then marketed by the Northern Chemical Association, H. C. Carel, President—was considered by the Council

in 1910. It was denied admission to New and Nonofficial Remedies because the therapeutic claims were unwarranted and because it was being exploited to the public. At that time, Benetol was found to be a liquid containing about 18 per cent. of the well known substance alphanaphthol, the solvent being a mixture of water, glycerin and soap.

In 1911 Benetol was advertised to the medical profession as well as to the public and was claimed to be a "marvelous medical discovery," "a new germicidal antiseptic marvel," "a chemical which destroys the germs of tuberculosis, typhoid, and cancer" (The Journal A. M. A., April 15, 1911, p. 1128). Benetol became a typical "patent medicine," and during the 1918 influenza epidemic the fear of the public was used as a means of promoting the sale of the product (The Journal A. M. A., Nov. 23, 1918, p. 1763). In 1920, the federal authorities charged with enforcement of the Food and Drugs Act held that the therapeutic claims made for Benetol were false and fraudulent and a judgment of forfeiture was entered by the court (The Journal, Nov. 6, 1920, p. 1285). Subsequently the federal authorities seized four shipments of Benetol Suppositories and in each case they were declared misbranded because of false and fraudulent claims. The government chemists found that these contained a mixture of alphanaphthol and betanaphthol.

Now (1923) acceptance of Benetol for New and Nonofficial Remedies has been requested by the Benetol Products Co., H. C. Carel, proprietor.

The present label for Benetol declares the product to contain "Inert ingredients; alcohol ½ per cent., glycerin 40 per cent., water 35 per cent.," but contains no information in regard to the identity or amount of the potent ingredient or ingredients.

In the advertising Benetol is stated to be "glycerite of naphthol" and in the information sent the Council, the product is stated to be "a 50 per cent. glycerite of naphthol in saponaceous solution with essential oils to improve taste." No information is offered to show whether the "naphthol" is the official betanaphthol or the alphanaphthol formerly contained in the product; nor is the amount declared.

In the advertising sent to physicians, Benetol is claimed to have a phenol coefficient of 1.35, to be a "powerful germicide," and because of the nontoxicity to be of "enormous value in internal medicine." The use of Benetol is proposed in a wide range of conditions, including even the recommendation for its use in "Intestinal Infections, Dysentery, Cholera, Typhoid, et al.," "'Ptomaine' Poisoning," "Indigestion," and "Internally as Kidney and Bladder Disinfectant."

Wrapped with the trade package is an advertising booklet intended for the public, which advertises Benetol and a number of Benetol products: Benetol Tooth Cream, Benetol Ointment, Benetol Catarrh Jelly, Benetol Nebulizing Oils, Benetol Powder for the Skin, Benetol Rectal Suppositories, and Benetol Suppositories for Women. The tenor of this booklet is to give a false idea of the effects which may be expected from the external or internal use of antiseptic or germicidal preparations. It contains many recommendations which are unwarranted and some which are pernicious.

The Council finds Benetol inadmissible to New and Nonofficial Remedies because (1) its composition is not declared (Rule 1) and (2) the therapeutic claims are unwarranted and constitute a detriment to the public health (Rules 4 and 6).

BISMUTH PREPARATIONS IN THE TREATMENT OF SYPHILIS

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., Aug. 25, 1923, p. 661

The Council has authorized publication of the following statement of the present status of bismuth preparations in the treatment of syphilis. W. A. PUCKNER, Secretary.

HISTORY

Balzer[1] was the first to make preliminary experiments to determine if bismuth could be used in the treatment of syphilis. He used bismuth citrate chiefly and abandoned his investigation when he found that bismuth compounds produced severe reactions in dogs, especially stomatitis and enteritis.

The investigation was again taken up by Sauton and Robert[2] who used a method similar to Ehrlich and Hata's experiments on the spirillocidal action of arsenical compounds. They studied the action of a so-called sodium tartrobismuthate in hens infected with *Spirochaetae gallinarum*. The results which are the real fundament of the later researches were sufficiently favorable to induce them to extend their work to syphilis and recurrent fever. The study was interrupted by the war and the death of Sauton.

Sazerac and Levaditi[3] continued the investigations and tested different compounds of bismuth and the metal itself in

1. Balzer, M. F.: Compt. rend. Soc. de biol. **41**: 537, 1889.
2. Sauton, B., and Robert, A. E.: Ann. Past. **30**: 261, 1916.
3. Sazerac, R., and Levaditi, C.: Ann. Past. **36**: 1 (Jan.) 1922.

experimental syphilis of rabbits and in trypanosomiasis. They recommended a compound, which they said was a sodium and potassium tartrobismuthate, for further tests in human syphilis.[4] Rabbits tolerated from 50 to 60 mg. of this drug per kilogram of body weight, when injected intramuscularly. The experimenters found 100 mg. to be the toxic dose, while 200 mg. proved lethal within from two to four days. The toxic effects of intravenous injections were in a striking contrast to the comparatively high dose tolerated intramuscularly. An intravenous injection of 5 mg. per kg. caused death. Whether the difference is due to the slow absorption after intramuscular injections of the drug, or to other causes is not known. The so-called *"curative dose"* of sodium and potassium tartrobismuthate in oil suspensions in syphilis of rabbits is at least 0.05 gm. per kg. of body weight, which is about one fourth of the lethal dose. Milian pointed out that the tolerated dose in man is much smaller than the sterilizing dose would be. The total amount which can be administered per kilogram in man in a period longer than a month hardly reaches the single minimal *"curative dose"* per kilogram in rabbits. The comparison of the effect of intramuscular injections of insoluble drugs is of course more difficult than of intravenous injections of arsphenamine and other drugs.

The first clinical tests were made by Fournier and Guenot[5] on 200 patients in different stages of syphilis, and the results were favorable. Numerous other authors have reported since on the effects of different preparations of bismuth in experimental and human syphilis, and the results obtained agree fairly. Among the more comprehensive reports are those by Klauder,[6] Hopkins,[7] and Pardo-Castello,[8] which may also be consulted for a more extensive review of literature.

The action on visible lesions in all stages of syphilis is distinct, though most of the authors admit that it is inferior to arsphenamine preparations. Neurosyphilis is also favorably influenced, though resistent cases are reported as with every other drug. Neurorecidives have not been observed so far, but the drug has not been used sufficiently to exclude

4. Bismuth tartrate compounds appear to have been first described by Schwarzenberg (Ann. Chem. Pharm. **61**: 244, 1847). Since then many chemists have prepared compounds of bismuth and tartaric acid. Sauton and Robert prepared their drug by the method given by Cowley (Chem. Drug. **82**: 212, 1913). Levaditi and Sazerac apparently prepared the compound which they called tartrobismuthate of sodium and potassium by the Cowley method, but without dissolving the precipitate (which is obtained in next to the last step of the operation) in sodium hydroxid.

5. Fournier, L., and Guenot, L.: Ann. Past. **36**: 14 (Jan.) 1922.

6. Klauder, J. V.: Arch. Dermat. & Syph. **7**: 721 (June) 1923.

7. Hopkins, J. G.: Arch. Dermat. & Syph. **7**: 745 (June) 1923.

8. Pardo-Castello, V.: Arch. Derm. & Syph. **7**: 586 (May) 1923.

such possibilities. It is generally agreed that the effect on the Wassermann reaction is slower than with arsphenamine. Some cases, however, which had remained positive in spite of treatment with arsphenamine and mercury, became negative after bismuth. Relapses occur.

UNTOWARD EFFECTS

Bismuth may cause a stomatitis characterized in milder cases by foul breath and a blue line on the gums. Pseudomembranes and ulcerations infected with fusiform bacilli and Vincent's spirochetes appear in severe cases. Enterocolitis is less frequent. Symptoms of slight lesions of the kidneys (polyuria, albuminuria) were observed. Severe nephritis is rare. Chills and fever sometimes follow the injections. While a rapid increase in weight has been observed after the first injections, prolonged treatment may cause loss in weight, headaches, fatigue and jaundice. It is a question if the increase in weight is a favorable symptom or whether it is due to retention of water by toxic action on the capillaries. Toxic exanthems have been reported.

METHOD OF USE

Fournier and Guenot recommend the administration of from 10 to 12 intramuscular injections of from 0.2 to 0.3 gm. of their "potassium and sodium tartrobismuthate" in oil suspension in about one month. The majority of other authors give smaller doses (0.1 gm.) or make longer intervals (4 days). Individualization is necessary, as everywhere. The interval between doses must be extended if the warning symptom of foul breath or other signs of intolerance appear. The resorption is not regular and may be checked by roentgenograms. After the course of from 10 to 12 injections one month of rest is given and the treatment may be repeated. Injections especially of higher doses are painful. Anesthetics may be added.

SUMMARY

1. Bismuth preparations have a sufficient experimental basis both for their favorable effects and limitations. The advantage consists in their distinct action on experimental syphilis. The limitations are clear, if one considers the disproportion between the large dose, which is necessary to sterilize an animal, and the small dose, which can be tolerated by man. The available information appears to show that bismuth preparations will not cure syphilis, when used alone.

2. Bismuth treatment is not usually injurious if the necessary precautions (observations for beginning stomatitis, examination of urine, etc.) are observed. Intravenous injection is to be strictly avoided. The therapeutic effect of bismuth is rated by the majority of authors between arsphenamine and mercury. Bismuth compounds may be valuable in cases in which the patients are intolerant to the other drugs used in the treatment of syphilis or resistant to them, as shown by a persistent positive Wassermann reaction.

C-O-M NOT ACCEPTED FOR N. N. R.

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., Aug. 11, 1923, p. 493

The Council has authorized publication of the following

W. A. PUCKNER, Secretary.

"C-O-M" is the proprietary, noninforming name under which the H. E. Frees Company, Chicago—claiming to be "nationally known chemists and bacteriologists"—exploits a preparation which is claimed to be the solution of magnesium citrate of the U. S. Pharmacopeia but to have the advantage over the official preparation in that it keeps indefinitely.

The advertising for C-O-M contains the unwarranted claim that magnesium citrate is "the one laxative which may be served to children as well as grown-ups." The advertising contains the assertion that "for colds, a half-glass at various times during the day is proper." By the phrase "for pneumonia, influenza, and bronchitis, as prescribed by your physician," it suggests that the use of magnesium citrate is curative in pneumonia, influenza and bronchitis.

The advertising, which is addressed to the public, suggests the indiscriminate and harmful use of laxatives by the statement that children may be kept in "rugged health" by giving a half-glass of C-O-M "whenever they seem indisposed in the least." We read further:

". . . If your head aches, and you feel tired and miserable, your system is clogged and your blood sluggish, you want a quick and easy elimination to relieve that dull, heavy feeling. You want prompt relief from what is recognized as the underlying cause of so much illness. A glass of Com will act promptly and quickly, and will overcome your indisposition."

It is asserted that "everyone should take a glass full of C-O-M at the slightest sign of a body disorder."

The Council refused recognition to C-O-M because (1) the application of a proprietary name to a pharmacopeial article is irrational and a detriment to rational therapy; (2) as a solution of magnesium citrate is readily prepared fresh and of standard quality by pharmacists, the claim for stability is not a sufficient warrant for the use of a proprietary name for an official article; (3) the therapeutic claims for C-O-M are unwarranted, and (4) the advertising propaganda is likely to lead to the excessive and ill-advised use of the preparation by the public.

CORYFIN NOT ACCEPTED FOR N. N. R.

Report of the Council on Pharmacy and Chemistry

The Council has authorized publication of the following report.

W. A. PUCKNER, Secretary.

Coryfin is the ethylglycolic acid ester of menthol. It is claimed to be superior to menthol in that it is better tolerated, has less odor, and its action is more prolonged.

Coryfin was accepted for New and Nonofficial Remedies in 1908, being then manufactured by the Farbenfabriken vorm. Friedr. Bayer and Co., Elberfeld, Germany, and marketed in the United States by Farbenfabriken of Elberfeld Co., New York. It was omitted from New and Nonofficial Remedies, 1920, because it was off the United States market. In 1920, the Winthrop Chemical Co. informed the Council that Coryfin was being manufactured in the United States and requested its reacceptance. Before readmitting Coryfin to New and Nonofficial Remedies, the Council examined the evidence for its therapeutic value. It was found that, though the article had been on the market for a number of years, it had attracted but slight notice and was not even mentioned in most text-books on pharmacology and therapeutics. In the absence of evidence for the therapeutic value of Coryfin and for its superiority over menthol, the Council voted not to readmit the product on the ground that, though it had been on the market for a considerable time, its usefulness had not been established.

Since extravagant claims were not made for Coryfin and the chief objection to its acceptance was the lack of proof that it is superior to menthol, the Council postponed the publication of its report on the nonacceptance of the drug to give the Winthrop Chemical Co. opportunity to obtain the needed evidence. This evidence has, however, not been supplied and accordingly the Council authorized publication of this report.

ESKOSAN AND ESKOSAN CUM METHYL SALICYLATE NOT ACCEPTED FOR N. N. R.

Report of the Council on Pharmacy and Chemistry

The Council has authorized publication of the following report. W. A. PUCKNER, Secretary.

Eskosan is claimed by the Esko Products Co., Phillipsburg, N. J., to be an ointment containing resublimed iodin, 3 per cent.; phenol, 2 per cent., and acetanilid, 8 per cent., in a base composed of pyrophyllite (a variety of aluminum silicate), wool-fat and petrolatum, perfumed with terpineol. All of the ingredients of Eskosan are claimed to be U. S. P. Eskosan cum Methyl Salicylate is claimed to have the same composition as Eskosan, except that it is "combined with 5 per cent. Methyl Salicylate, U. S. P." In the advertising Eskosan is referred to as "The Iodin Ointment." The trade package of Eskosan bears the declaration that the product "embodies free iodin, acetanilid, phenol and lanolin with a neutral base." The trade package of Eskosan cum Methyl Salicylate bears the declaration that this product "embodies free iodin, acetanilid, phenol, methyl salicylate and lanolin." The claims, however, that Eskosan is an "iodin ointment," that it contains 3 per cent. of resumblimed iodin, and that it and Eskosan cum Methyl Salicylate embody free iodin are not justified, as shown by the report of the A. M. A. Chemical Laboratory which follows:

A specimen of Eskosan and one of Eskosan cum Methyl Salicylate sent to the Council by the Esko Products Company were each tested for the presence of free (uncombined) iodin. Eskosan did not respond to the usual tests for free iodin, while Eskosan cum Methyl Salicylate showed that about 0.11 per cent. of uncombined iodin was present. It is well known that iodin combines with phenol (Rheumaticide, Rep. A. M. A. Chem. Lab. **6**:37, 1913; Iocamfen and Iocamfen Ointment, Rep. A. M. A. Chem. Lab. **9**:118, 1916), and hence the manufacturer should know that his combination is not an iodin ointment, and that it does not contain any appreciable amount of free iodin.

A circular which accompanies the trade packages of Eskosan and Eskosan cum Methyl Salicylate (and thus advertises these products to the public) contains the assertion that "Iodin, phenol, and acetanilid is a most happy combination" and that "their joint action" is "enhanced by the presence of a Neutral Base and the use of pure lanolin as an unguent." It is asserted that Eskosan is a rational application in the

following conditions: "Diseases and Injuries of Joints—arthritis and synovitis (acute and chronic), sprains (acute and chronic), thecitis, tendosynovitis, bursitis, fibrous ankylosis." The use of Eskosan is also proposed in "Skin Lesions—eczema, psoriasis, ringworm, herpes zoster, dermatitis," in "lymphangitis (acute and chronic), adenitis (acute and chronic), chronic tuberculosis adenitis, mastitis, parotiditis, orchitis," and as a topical application in "glandular disturbances," such as "tonsilitis, pharyngitis, parotiditis." Its use is also advised in "phlebitis (traumatic or infectious)," "lumbago," "hemorrhoids, rectal fissure, pruritis ani." Eskosan cum Methyl Salicylate is stated to be "especially applicable in the treatment of rheumatic arthritis and kindred conditions." These therapeutic claims are without warrant; the indefinite composition of these products and their complexity prevent their rational use in cases in which the external application of an iodid preparation or of methyl salicylate is indicated.

Eskosan and Eskosan cum Methyl Salicylate are inadmissible to New and Nonofficial Remedies because (1) their composition is not correctly declared (Rule 1); (2) they are advertised in a way to lead to their ill-advised use by the public (Rule 4); (3) they are marketed with unwarranted therapeutic claims (Rule 6); their names are not descriptive of their composition (Rule 8); and (4) they present mixtures of drugs the use of which is irrational and a detriment to rational therapy (Rule 10).

ETHYLENE AS AN ANESTHETIC

Preliminary Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., April 7, 1923, p. 1003

The Council has authorized publication of the following statement on the experimental status of ethylene in medicine.

W. A. PUCKNER, Secretary.

A report on "The Physiologic Effects of Ethylene—a New Gas Anesthetic," by A. B. Luckhardt and J. B. Carter, was published in THE JOURNAL, March 17, 1923, p. 765.

Ethylene is a well known substance chemically, having the formula $CH_2 : CH_2$. At room temperature and ordinary pressure it is a gas slightly lighter than air; it is not very soluble in water, is more soluble in alcohol, but is soluble in ether. A mixture of ethylene and oxygen explodes when

brought in contact with a naked flame. It is solid below —169.4 C., and boils at —103.9 C. It is generally prepared from alcohol by a so-called dehydrating action. The product reported in the paper was prepared by interaction of alcohol and orthophosphoric acid. So far neither the product prepared by the authors nor any commercial product has been examined in the A. M. A. Chemical Laboratory. As soon as a satisfactory market product is found, standards of purity will be elaborated.

The animal experiments reported by Luckhardt and Carter indicate that ethylene has a direct action on the nervous system when a concentration of 90 per cent. is used; that the motor reflexes are abolished at this concentration, and that the phenomena produced by the undiluted gas are partly asphyxia, which factor can be removed by the addition of oxygen, when it is seen that narcosis results from the ethylene itself. The authors believe that the ethylene does not react with the hemoglobin of the blood.

The trials carried out by Luckhardt and Carter on human subjects appear to confirm the anesthetic value of ethylene, as demonstrated on animals. Their experiments indicate that deep surgical anesthesia can be induced without marked unpleasantness. Analgesia is reported to come on easily and apparently long before surgical anesthesia is established. The authors believe, as a result of the experiments, that ethylene will be found more desirable than nitrous oxid, because of its ease of administration and rapid recovery after long continued administration. However, the anesthetic results reported have been only on persons in normal health.

The available evidence for the value of ethylene as a new anesthetic is thus far limited to the report mentioned. Particular attention is called to the conclusion of the authors: "This must be considered as a preliminary report of experimental work which has not been carried far enough to warrant general clinical use." In view of this, the Council considered the report and recommended that confirmation of the work obviously is necessary before more than a tentative acceptance of ethylene can be accorded. Nevertheless, it is recognized that the status of ethylene as an anesthetic is such as to warrant further research with the substance; as preliminary to such research the quality of the product, particularly absence of toxic impurities, must be determined. The Council has deferred acceptance of ethylene for New and Nonofficial Remedies until proof has been furnished that the product is a useful addition to the list of already accepted anesthetics, and until a satisfactory product is on the market.

FERRO-NUX COMP. NOT ACCEPTED FOR N. N. R.

Report of the Council on Pharmacy and Chemistry

The Council has authorized publication of the following report. W. A. PUCKNER, Secretary.

"Ferro-Nux Comp." is put on the market by the American Drug Company, Inc., Boston. According to the manufacturer:

"Each fluid ounce represents Tr. Iron Citrochloride 10 min., Tr. Nux Vomica 6 min., Fowler's Solution 1 min., Sodium Bromide 6 grains, F. E. Cascara 8 grains, Tr. Gentian Comp. 6 min., Aromatic Elixir, Syrup, Water, Alcohol Contents 11%."

The label on this irrational mixture of iron, nux vomica, arsenic, gentian, cascara bromid and alcohol declares that it "is an ideal combination and general tonic of choice in anemia, chlorosis, tuberculosis, malnutrition and nervous exhaustion." Such therapeutic recommendations, while they may lead the public to use the product, are an insult to rational medicine. Yet the American Drug Company avers that its purpose is to manufacture and distribute approved scientific medicinal preparations and that its products are in no wise "patent medicines." The name, "Ferro-Nux Comp.," is insufficiently descriptive of the composition of the mixture and, since alcohol is no doubt the most potent single constituent, the name is misleading.

Ferro-Nux Comp. is inadmissible to New and Nonofficial Remedies because: (1) the therapeutic recommendations for its use are unwarranted and constitute an indirect advertisement to the public; (2) the preparation is marketed under a name which fails to declare its potent ingredients and (3) it is an irrational, unscientific mixture and its use is a detriment to rational therapy.

FLEISCHMANN'S YEAST NOT ADMITTED TO N. N. R.

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., May 12, 1923, pp. 1398-1399

The Council has authorized publication of the following report. W. A. PUCKNER, Secretary.

In March, 1921, the Council took up the consideration of Fleischmann's Yeast on account of the extensive and extreme therapeutic claims which were made for this preparation. Since then the Council has given much attention to the sub-

ject of yeast therapy. The chairman called in consultation eminent students of nutrition and clinicians qualified to speak with authority on questions of nutrition, dietotherapy and pediatrics. The object was to determine whether the effects of yeast and yeast preparations on animals deprived of food containing vitamin B gave promise of having important therapeutic application. After a comprehensive discussion it was concluded that there is little likelihood that the administration of yeast or yeast preparations representing vitamin B concentrates will be of therapeutic value in many cases for which they are advertised. The view that there was no satisfactory evidence in favor of the therapeutic administration of yeast in most conditions for which it is advertised was concurred in by many of those who have contributed to the laboratory reports of the action of yeast or its vitamin in experiments on animals previously deprived of the growth-promoting constituents present in many foods and in yeast.

As a result of its inquiry, the Council adopted (The Journal A. A. M., April 15, 1922, p. 1146) the following principles to guide in the consideration of yeast preparations and vitamin B concentrates:

1.—The claim that deficiency of vitamin B and diseases resulting therefrom are common conditions in the United States is not at this time supported by adequate, acceptable evidence.

2.—The claim that yeast preparations or extracts are, in principle or in general, essentially more effective or more practical or more available means of administering vitamins than the commonly available vitamin-containing foods is not at this time supported by adequate, acceptable evidence.

3.—The claim that therapy with yeast or yeast preparations has as yet more than an experimental status is not at this time supported by adequate, acceptable evidence.

Further, the Council has adopted (The Journal A. M. A., July 8, 1922, p. 135) an article on yeast preparations for inclusion in New and Nonofficial Remedies in which, among other things, it is pointed out (1) that the opportunities to obtain vitamin B through the customary foods are so abundant as to make the demand from special sources of the vitamin limited at the present time; (2) that yeast is a mild laxative, but that the cause of this laxative action has not been determined so far as one can learn; (3) that the supposed beneficial effect of yeast administration on furuncles, acne, etc., lacks substantiating evidence; (4) that such laxative effects

may be expected from an anticonstipation agent; (5) that it is not clear whether live cultures of yeast may be used to change the intestinal flora, if indeed such reaction becomes desirable, and (6) that many of the conditions for which yeast and yeast preparations have been proposed are so variable in their clinical courses and so likely to show improvement without special treatment that the elaborate claims that are made for yeast therapy for somewhat indefinite disorders must be largely discounted.

Many advertisements for Fleischmann's Yeast are misleading in that they tend to create the belief that many diseases are prevented or cured by its use. Advertisements addressed to the medical profession, through one-sided quotations, are likely to lead physicians to believe that the efficacy of yeast therapy in many conditions has been established. Advertisements addressed to the public are bound to create the opinion in the mind of the lay reader that reliance may be placed on yeast in many conditions which call for therapeutic treatment, the neglect of which may often lead to serious and even fatal consequences.

A booklet which is offered "free, to physiological chemists, physicians and hospitals," the phraseology of which creates the impression of being scientific and conservative in tone, asserts that "dentists have used yeast to advantage in pyorrhea, supplementing the necessary local treatment," whereas it has been generally acknowledged that internal medication has not been found to influence the course of pyorrhea. It is asserted in this booklet that a "frequent cause of general debility is lack of a sufficient quantity of vitamin B in the diet." This is contrary to the conclusions arrived at by the Council, as stated under (1) in the report quoted above from The Journal A. M. A. of April 15, 1922.

Fleischmann's Yeast is advertised directly to the laity for the relief of boils:

"For pimples or boils eat 1 to 3 cakes of Fleischmann's Yeast a day."

The patient who treats himself for boils in this manner may later die of a carbuncle as the result of the neglect of proper treatment. Many of the advertisements cite experiments of well-known physicians who reported that sixty-six patients improved, or were cured, during the use of Fleischmann's Yeast in a total of seventy-six patients suffering with furunculosis, acne vulgaris, acne rosacea, constipation, gastro-intestinal catarrh, intestinal intoxication, eczemas, arthritis deformans, psoriasis, erythema and urticaria, bronchitis, urethritis, pruritus, folliculitis, conjunctivitis, duodenal ulcer and swollen glands. It is not at all remarkable that

skilled physicians could choose so many patients who were suited for treatment by almost any means, for it is very well known that an equal number of patients suffering from these diseases could be chosen who would improve without any medication whatever, provided that suitable hygienic and dietary measures were observed. On the other hand, there is no evidence that Fleischmann's Yeast yields any better results in the majority of patients suffering with these disorders than are obtained with exactly the same treatment minus the yeast.

One advertisement contains the following:

"You who do the work of the world in the sweltering heat of the summer need food that nourishes but does not overheat. Fleischmann's Yeast added to your diet builds vitality, power and endurance. Eat two to three cakes a day and see how they increase your ability to withstand summer heat. You will also desire less of the rich, heat-producing foods that make you uncomfortable in your summer work."

If this means anything it means that Fleischmann's Yeast contributes energy, in important amounts, to those who do hard work. A cake of yeast weighs half an ounce and contains protein, fat, and glycogen sufficient to yield approximately 12 calories, or less than one-half of one per cent. of the energy requirement of one who does hard work; yet yeast is advertised as an ideal food. It might as well be argued that as coffee will cause a little child to "desire less of the rich, heat-producing foods that make you uncomfortable in your summer work," one would be justified in recommending an abundance of coffee for a little child!

The statement that "People who are adding Fleischmann's Yeast to their daily diet find that their body functions are kept normal and regular," is manifestly incorrect. It is general and inclusive. It does not say that some people find this to be the case, but it makes the comprehensive and inclusive statement that, in general, those who add it to their diet obtain this result. If it were true, then no one who added the yeast to the diet would become ill. Such a statement is obviously absurd. If, as claimed, it was made by a prominent physician, then, evidently, even prominent physicians may make careless statements.

An example of the misleading character of the advertisements for Fleischmann's Yeast without direct falsehood is afforded by the following:

"*When the plane of metabolism first must be raised.*—Hundreds of experiments in animal nutrition have proved the great value of yeast in the growth-producing dietary. One of the most striking descriptions of its importance is given by a man pre-eminent in the field of physiological chemistry: 'A scrawny, lethargic animal, rapidly dwindling in

size, with unsleek coat and evident malnutrition, will completely change its appearance and responses in a few days at most on a diet unchanged except for a tiny bit of yeast.' "

That statement is not deliberately false, but taken without the context it is false. The previous diet of the "scrawny, lethargic animal" had been deliberately chosen for experimental purposes with a view to depriving the animal of one constituent which is present in a great variety of foods—and in yeast. One might conduct wholly analogous experiments in which anemic animals were deprived of food containing iron (rice and sugar, for instance, are free of iron) and by the addition of almost any suitable food known to contain iron, he could in a short time cause striking changes in the animal's condition. The advertisment is misleading in that it gives the impression that yeast is essential for this remarkable change in the condition of the animal. As a matter of fact yeast is merely one of a large number of the commonest articles of the daily diet that contain this vitamin.

The Council voted to refuse recognition to Fleischmann's Yeast (1) because it is advertised by means of unwarranted and misleading therapeutic claims and (2) because it is advertised to the public with unwarranted therapeutic claims that might become a detriment to the public health.

GLYCO-PEPTO MILK NOT ADMITTED TO N. N. R.

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., April 21, 1923, p. 1165

The Council has authorized publication of the following report.

W. A. PUCKNER, Secretary.

Glyco-Pepto Milk is a sour milk said to contain *Bacillus bulgaricus, Streptococcus lacticus* and *Glycobacter peptolyticus.* It is marketed by the Glyco-Pepto Manufacturing Co., Inc., Long Island City, N. Y., with the claim that its administration supplemented with a potato diet, through the presence of *Glycobacter peptolyticus,* permits the implantation of the Bulgarian bacillus in the lower intestine and thus brings about an almost complete disappearance of phenols and indol from the urine.

Glycobacter peptolyticus has some amylolytic action; in flask cultures, in the course of fourteen days, about 40 per cent. of the starch is converted into sugar. It has been claimed that the administration of this organism in man

produces a similar effect. There is no evidence, however, to show how great the amylolytic action would be in a few hours either in a flask or in the intestines. The claim that *Glycobacter peptolyticus* converts the starch into sugar and thus permits the implantation of *Bacillus bulgaricus* in the large intestine rests on very indirect evidence, and is open to question.

The experimental work used as a basis is that of Metchnikoff and Wollman, published in 1912. In their publication these authors devote only a little more than one page of text to the work with *Glycobacter peptolyticus* in rats and in man. They state that the administration of this organism caused the phenols and indoxyl to disappear from the urine in some rats; in others the effect was less complete but, nevertheless, marked; in rare cases the effect was nil; further, that the most marked effect was observed with four persons who took potatoes with *Glycobacter*. The tabulated results obtained with rats and man are by no means so conclusive as the authors, in their optimism, believe. In two instances in which marked diminution is given, typographic errors are involved. The claims for the combination of *Glycobacter peptolyticus* with *Bacillus bulgaricus* are based on a single experiment of these authors with eleven rats. This experiment is of little value, since in the fifty-three days preceding the administration of mixed culture the phenols dropped from 0.037 to 0.011, and the indoxyl from 0.086 to 0.006 gm. per liter of urine. The subsequent drop on treatment with the mixed bacteria for five days, of phenol to 0.005 and of indoxyl to nondeterminable amounts may have been a continuation of the decline due to the diet. Yet the authors, although they noticed the marked decrease due to the diet, concluded that it was only after the administration of the bacteria that the almost complete disappearance of the phenols and indoxyl was obtained. Although ten years have elapsed since the preceding results of Metchnikoff and Wollman were published, the Glyco-Pepto Manufacturing Company has submitted no confirmatory evidence.

According to the manufacturers of Glyco-Pepto Milk, the therapeutic indications for this product are:

"As a disinfectant to the digestive tube and regulator of the stools."

"In enteritis, infant diarrhea, and chronic disturbances of the gastro-intestinal tract."

"In ulcerations of the stomach, in cutaneous diseases due to digestive troubles."

"After surgical interventions of the digestive tube, after accouchements, in tuberculosis, anemia and general debility."

These claims appear to be based on the testimonials of Swiss physicians, who refer to the usefulness of the product as "agreeable food," "exquisite in flavor," "easily taken," etc. The preparation may be a pleasing beverage and light food, but there is no acceptable evidence for the many therapeutic claims that are made.

The Council declares Glyco-Pepto Milk inadmissible to New and Nonofficial Remedies.

GLY-SO-IODONATE

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., Dec. 22, 1923, p. 2123

The Council has authorized publication of this report.

W. A. PUCKNER, Secretary.

In July, 1921, Charles E. Huchings requested consideration of Gly-So-Iodonate. He claimed to be a graduate of King's College of Medicine, London, but the registrar of that institution has written that his name does not appear on the college's medical register. The product, said to be a "chemical germicide-antiseptic," was "owned and controlled exclusively by the Wisconsin Medical Laboratory" which is at the present time claimed to be affiliated with the National Medical Research Laboratories, Milwaukee, Wis.

The composition of Gly-So-Iodonate was originally stated to be:

	Per Cent.
"Double distilled water	81
Alcohol	10
Glycerin	2
Solids	7
Percentage of solids as follows:	
Sodium Carbonate	2.50
Sodium Chlorid	1.60
Sodium Sulphate	0.65
Sodium Bicarbonate	0.40
Potassium Carbonate	0.15
Alumina Oxid	0.05
Calcium Sulphate	0.10
Magnesium	0.05
Boracic Acid	0.30
Potassium Iodid	0.30
Iodin	0.40
Corrosive Sublimate	0.50"

The method of preparation was given as follows:

"Composition and chemicals used in the preparation of Gly-so-iodonate; First Part:

Sodium Carbonate	36.00
Sodium Chlorid	23.00
Sodium Sulphate	10.06
Sodium Bicarbonate	6.02
Potassium Carbonate	2.18
Alumina Oxid	1.50
Calcium Sulphate	2.72

Magnesium Sulphate	1.52
Boracic Acid	5.00
Potassium Iodid	5.00
Iodin	7.00

"The method of completing the solution is as follows, Second Part: 3,219 c.c. of double distilled water is brought to a boiling point of 225 degrees (F). After boiling for a period, 20 grains of corrosive sublimate is added—solution is again held at boiling point, then the fused chemicals (part one) is added—boiling is again held for a period, after which the whole is submitted to a special process of distillation. After cooling to a certain degree determined by years of trials, 450 c.c. of 190° alcohol is added—again distilled, and the 115 c.c. of C. P. glycerin is added—final process is another special distillation for bottling."

"The above quantities are used for making one gallon."

The Council considered the information, and the following points were presented to the Wisconsin Medical Laboratory:

I. *Composition Not Correctly Declared.*—Obviously the formula presented was an impossible one: (1) any free iodin added in accordance with the formula would react with the alkali carbonate to yield alkali iodid and alkali iodate, and (2) mercuric chlorid would react with alkali iodids to give an alkali mercuric iodid. Gly-So-Iodonate, moreover, was referred to as a distillate, for in the process of manufacture, as submitted, the solids of the formula were dissolved in water, the solution distilled and the glycerin and alcohol added to the distillate. It was safe to predict that, no matter what the interactions of the ingredients may have been, the salts of sodium, potassium, magnesium, calcium, etc., would not be sufficiently volatile to permit their distillation with the water vapors.

II. *Formula Needlessly Complex and Irrational.*—The finished Gly-So-Iodonate, a "non-poisonous" "distillate," according to the submission of the manufacturer, was a product "presenting and maintaining a dual duty of germicide and healer." It was said not to be deteriorated by "light waves, sun rays, heat and cold" and it was claimed, furthermore, that "the various chemicals are so arranged to either [sic] take up all tissue fluids and hold them in suspension, against growth, or dry up unessential exudates," "each [chemical] fulfilling a specific action within the exudates and sebums common with most wounds." In the end no evidence was submitted to demonstrate the superiority of the mixture over that of a solution of the well-known potassium mercuric iodid of equivalent concentration.

III. *Label Not Acceptable and Name Not Descriptive.*—The amount of poisonous material, mercury compound (potassium mercuric iodid?) in a given quantity was not declared on the label and the name Gly-So-Iodonate is not descriptive of the potent ingredient of the mixture.

The manufacturing company made a reply to this report, but the reply contained no statement of facts which altered the conflicts of Gly-So-Iodonate with the rules which govern the acceptance of products for inclusion in New and Non-official Remedies.

RECENT DEVELOPMENTS

From recent developments, it is evident that an active selling campaign for Gly-So-Iodonate is being directed toward factories and large commercial concerns by the National Medical Research Laboratories. The original Gly-So-Iodonate, with its statement of composition but slightly changed, is now claimed to be the base of three additional products supplied by the same firm—"Iomer-Mensal for nose and throat work, Saline-Merammo for genito-urinary work, and Gly-So-Dental for dentistry and mouth wash."

GLY-SO-IODONATE

Volume

	Per Cent.
Distilled Water	79
Alcohol	10
Glycerin	4
Minerals, Alkaloids, etc.	7

Per Cent. of Minerals, Alkaloids, Etc.

Corrosive Sublimate	0.75
Iodin	0.55
Chlorids	2.10
Vegetable Alkaloids	2.05
Platinum	0.45
Potassium Salts	1.10

In reference to the last mentioned products, a notice appears on the present-day label of Gly-So-Iodonate, which reads, "CAUTION-G. S. I. is especially prepared for surgical work and for all infections other than found in Ear, Nose and Throat or Genito-Urinary tract. Our various fluids are not interchangeable."

Specimens of Gly-So-Iodonate and the allied products were recently obtained in the open market, and the statements of composition of these are herewith reprinted from the labels. A glance suffices to show the incomplete and meaningless statements of composition. A comparison of the claimed composition of the products shows them to be complex mixtures varying slightly in the amount of this or that and with new ingredients added at will. The three new products have the potassium salts, stated to be in Gly-So-Iodonate, omitted; all show an increase over Gly-So-Iodonate in chlorid content and iodin (a claimed iodin increase of 2.55 per cent. in the case of Saline-Merammo). A few new ingredients are declared, such as, small amounts of sodium and ammonia in

Saline-Merammo, sodium and magnesium in Iomer-Mensal, and sulphids in Gly-So-Dental. All four products have one property in common: On opening a bottle, there is a distinct odor of iodoform, evidently due to the interaction of iodin and alcohol in alkaline solution.

Gly-So-Iodonate, the so-called base of the other preparations as now marketed, is claimed to differ from that formerly sold in that (1) in the new product there is an alleged increase of both mercuric chlorid and iodin; (2) unnamed chlorids and unnamed potassium salts are now claimed instead of the defined sodium and potassium salts, alumina oxid, etc.; (3) platinum is claimed as a new ingredient of the product, and (4) contrary to known principles of compatibility, vegetable alkaloids are claimed as new ingredients.

IOMER-MENSAL		SALINE-MERAMMO		GLY-SO-DENTAL	
Volume		Volume		Volume	
	Per Cent.		Per Cent.		Per Cent.
Distilled Water	74.50	Distilled Water	73	Distilled Water	76
Alcohol	11.50	Alcohol	11	Alcohol	9.50
Glycerin	4.50	Glycerin	4	Glycerin	5.50
Minerals, Alkaloids, etc.	9.50	Minerals, Alkaloids, etc.	12	Minerals, Alkaloids, etc.	9
Per Cent. of Minerals, Alkaloids, etc.		Per Cent. of Minerals, Alkaloids, etc.		Per Cent. of Minerals, Alkaloids, etc.	
Corrosive Sublimate	0.30	Corrosive Sublimate	0.81	Corrosive Sublimate	0.60
Iodin	1.05	Iodin	3.10	Iodin	0.75
Vegetable Alkaloids	2.15	Sodium	0.74	Chlorids	4.80
Platinum	0.10	Ammonia	0.30	Vegetable Alkaloids	1.50
Chlorids	3.70	Vegetable Alkaloids	2.15	Platinum	0.25
Sodium	1.25	Chlorids	4.50	Sulphids	1.10
Magnesium	0.75	Platinum	0.40		

No statement is made as to why platinum, which has found no use in medicine, is desirable, or as to why it is claimed to be present in a quantity of nearly one half of one per cent. Obviously, there could hardly be present the alleged 0.45 per cent. either of platinum or of a salt of platinum, for this amount in one quart alone would be worth at the present market price over fifteen dollars, a sum between three and four times as great as that asked for Gly-So-Iodonate itself.

In view of the improbability of these claims, the Chemical Laboratory of the American Medical Association made the following determinations on Gly-So-Iodonate:

	Per Cent. By Weight
Vegetable alkaloids	0.001
Mercury	0.026
Mercury (0.026%) Calculated as Mercuric Chlorid (Corrosive Sublimate)	0.036
Platinum ..... less than	0.01

The above analysis confirmed the suspicion that there were no alkaloids present; mercury was present in less than one-twentieth of the claimed amount, and platinum was present in less than one forty-fifth of the asserted amount!

The original objection that the name of the product is not suggestive of the most potent ingredient still holds. The analysis made in the laboratory showed that there was no free iodin, but combined iodin, in the form of iodid and iodate. A commonly used method for the extemporaneous preparation of potassium mercuric iodid is to mix mercuric chlorid with potassium iodid. In view of this, and in consideration both of the statements made on the new and the old labels, and the findings of the association's laboratory, it is evident that the mercury contained in Gly-So-Iodonate is present in form of a complex salt such as potassium mercuric iodid and not as "corrosive sublimate" as declared. No complex compound of mercury is mentioned in the statement of composition; instead the asserted presence of free iodin is stressed, and the name itself is suggestive of iodin rather than mercury.

In the advertising that is being sent to commercial concerns, the National Medical Research Laboratories make many claims for the superiority of Gly-So-Iodonate and its allied products:

> G-S-I is, we feel, the BACTERICIDE the medical world has searched for since the days of LISTER.
>
> Indicated in every case which formerly called for Iodine, Phenol, Silver Nitrate, or Caustics.
>
> G-S-I is a bactericide of enormous potency. Its effect upon tissues is salubrious. Its application is simple, clean, non-irritating and not involved in the tedious, expensive and complicated technique of other antiseptics. Its recent discovery makes its far reaching possibilities as yet unknown, and much of its amazing promise is still in the hands of the pioneers in its use.

It is claimed that many Milwaukee firms are users of the product. There are also reprinted letters of recommendation from general managers, safety engineers, and even from a nurse and a physician of these commercial plants. These recommendations are of the unscientific and uncritical type common to such testimonials.

To summarize; Gly-So-Iodonate is not the scientific masterpiece it is claimed to be; the statement of composition is obviously incorrect; the product is essentially semi-secret; its actions are virtually those of a solution of potassium mercuric iodid to which has been added a chemical hodge-podge; it is marketed under a nondescriptive and misleading name. In view of these facts, the Council has authorized publication of this report declaring Gly-So-Iodonate inadmissible to New and Nonofficial Remedies.

HERRADORA SPECIALTIES NOT ACCEPTED FOR N. N. R.

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., April 28, 1923, pp. 1259-1260

The Council has authorized publication of the following report.

W. A. PUCKNER, Secretary.

Early in 1922 the Scientific Chemical Co., New York (Marco Aurelio Herradora, M.D., President), requested the Council to consider its intravenous preparations. The firm sent the proof of a proposed booklet which contained extravagent claims for intravenous therapy in general and for the Herradora specialties in particular, and also a typewritten manuscript, "Digitalis Compound (Herradora) for Intravenous Use," with a request that anything therein which conflicted with the rules of the Council be brought to its attention. The firm also sent specimens of the following preparations:

Herradora's Arsenic Compound for Intravenous Use, Nos. 1 to 6.
Herradora's Arsenic and Hypophosphites for Intravenous Use.
Herradora's Arsenic and Iron Compound for Intravenous Use.
Herradora's Calcium Compound for Intravenous Use.
Herradora's Calcium-Sodium-Glycerophosphate Compound for Intravenous Use.
Herradora's Chlorids Compound for Intravenous Use.
Herradora's Chlorids with Iron Compound for Intravenous Use.
Herradora's Creosote Compound for Intravenous Use, Nos. 1 and 2.
Herradora's Digitalin Compound.
Herradora's Glycerophosphate-Iron and Nickel Compound for Intravenous Use.
Herradora's Guaiacol Compound for Intravenous Use.
Herradora's Iodids Compounds for Intravenous Use.
Herradora's Hexamethylenamin and Guaiacol Compound for Intravenous Use.
Herradora's Iron, Manganese and Nickel Compound for Intravenous Use.
Herradora's Mercury Compound for Intravenous Use.
Herradora's Quinin Compound for Intravenous Use, Nos. 1 and 2.
Herradora's Sodium Iodid for Intravenous Use.
Herradora's Sodium Iodid-Salicylate-Guaiacol Compound for Intravenous Use.

These, in addition to the names of the preparations and the "formulas," bore—with a few exceptions—the following ambiguous and questionable statement:

"Special aseptic, sterilized and antiseptic bland mutual dissolvent to make 20 Cc. Drugs herein contained have been modified perfecting their purity to regulate toxicity, thus insuring safe and higher efficiency."

The proposed advertising was apparently written by one whose knowledge of therapeutics was a mixture of the latest enthusiasm for intravenous therapy and the most archaic pharmacologic tenets. Its style was bombastic and pseudo-scientific. The material abounded in unwarranted and unsubstantiated statements in favor of intravenous administration of drugs and for the use of complex mixtures of drugs. The preparations bore, in many cases, a striking resemblance to "intravenous" preparations which had been previously reported on unfavorably. In view of this fact and the firm's statement that it desired to remove any claims objectionable to the Council, the objections to the advertising were pointed out in a general way, and the firm was supplied with reports of the Council dealing with similar preparations.[1] Since some of the products contained hypophosphites and glycerophosphates,[2] Council reports which set forth the lack of evidence for the therapeutic use of these were also sent.

In September, the firm sent a revision of parts of the booklet and of the whole manuscript on "Digitalis Compound (Herradora) for Intravenous Use." This revision was not satisfactory. As before, this advertising made claims for intravenous medication that are fundamentally opposed to modern therapeutic teachings. The tenor of the entire matter was to discredit the oral administration of drugs and to substitute intravenous medication as a routine. The fundamental objections to it with specific illustrations of unwarranted statements were a second time brought to the attention of the firm. Since then the firm has not supplied the Council with any evidence to indicate that a genuine effort is being made to remove the objections.

On the other hand, the Council learned that the firm was making efforts to secure the use of its preparations by physicians and in hospitals. On Dec. 20, 1922, a physician received advertising from the firm which was almost a verbatim copy of parts of the booklet originally submitted. This advertising is evidently a reprint with minor changes which do not alter the original meaning.

SOME RECENT CLAIMS

The following, quoted from the present advertising circular "Syphilis, Its Treatment" illustrates the character of the claims advanced for the Herradora specialties:

1. Venarsen, Report Council Pharm. & Chem., J. A. M. A. **64**: 1780 (May 22) 1915; Venosal, Report Council Pharm. & Chem., J. A. M. A. **70**: 48 (Jan. 5) 1918; Some of Loeser's Intravenous Solutions, Report Council Pharm. & Chem., J. A. M. A. **76**: 1120 (April 16) 1921.

2. The Therapeutic Value of Glycerophosphates, Report Council Pharm. & Chem., J. A. M. A. **67**: 1033 (Sept. 30) 1916; The Hypophosphite Fallacy, Report Council Pharm. & Chem., J. A. M. A. **67**: 760 (Sept. 2) 1916.

"The arsenic compound presented here has been completely dimethylized, readily diffusible, while its organic structure is still retained. As such it may be described as a harmonized chemical medium between the plain cacodylate and dioxi-diamino type of arsenicals. It is prepared in six ascending strengths which will be hereafter described. It has been prepared for the treatment of syphilis or any other *trypanosome disease* where the maximum dose of arsenic is required. These arsenic compounds which I have prepared are regarded as superior to any other form of organic arsenic for the treatment of syphilis now in use."

According to the label on the specimens sent to the Council, Herradora's Arsenic Compound for Intravenous Use, No. 1 contains: "Arsenic-Organic Compound, Equivalent to Sodium Dimethylarsenate (As 1½ grains) 5 grains; Mercuric Iodid, 1/13 grain; Arsenic Iodid, 1/8 grain." The other forms, Nos. 2 to 6 inclusive, are claimed to contain the same amounts of mercuric iodid and of arsenic iodid but progressively increasing amounts of the "arsenic-organic compound; equivalent to sodium dimethylarsenate," the arsenic element of which, according to the formulas, varies from 30 per cent. to 34.84 per cent. So far as the statements go, the character and the composition of the "arsenic-organic compound" are not declared and the preparations may be regarded as secret in composition. The language of the advertising, however (particularly the claimed freedom from untoward effects), the amount of drug in a dose, and chemical behavior of the solutions strongly suggest that in Herradora's Arsenic Compounds we have another sodium cacodylate preparation patterned after Venarsen,[3] on which the Council reported in 1915 and which has been a pattern[4] for similar products put out by firms specializing in intravenous therapy.

In the "arsenic-organic compound" in Herradora's Arsenic Compound *is* sodium cacodylate (sodium dimethylarsenate), then the claims for its efficacy are unacceptable, for sodium cacodylate has been found without effect on experimental trypanosomiasis and inefficient in the treatment of syphilis.[5] If the "arsenic-organic compound" *is not* sodium cacodylate

3. Venarsen, Report Council Pharm. & Chem., J. A. M. A. **64**: 1780 (May 22) 1915.

4. "Arsenoven S. S." and "Arseno-Meth-Hyd," Report Council Pharm. & Chem., J. A. M. A. **73**: 353 (Aug. 2) 1919.

5. Cole, H. N.: A Study of Sodium Cacodylate in the Treatment of Syphilis, J. A. M. A. **67**: 2012 (Dec. 30)) 1916; Sodium Cacodylate in the Treatment of Syphilis, Correspondence, J. A. M. A. **68**: 390 (Feb. 3) 1917; Sodium Cacodylate in the Treatment of Syphilis, Correspondence, J. A. M. A. **68**: 566 (Feb. 17) 1917; Pharmacology of Arsenicals, Current Comment, J. A. M. A. **76**: 595 (Feb. 26) 1921; Mon-Arsone Not Admitted to N. N. R., Report Council Pharm. & Chem., J. A. M. A. **76**: 1781 (June 18) 1921.

then the claims are unacceptable because they are made for a compound of secret composition for which there is no evidence of therapeutic worth other than the assertions of the manufacturer. In any case, it is irrational to administer an organic arsenic compound in combination with mercuric iodid and an inorganic arsenic compound. It should be mentioned in passing, that while the preparation is claimed to contain arsenic iodid, this compound (AsI_5) does not exist, and arsenous iodid ($As\ I_3$) is decomposed in aqueous solution into arsenous acid and hence arsenic iodid is probably not contained in the solution.

INADMISSIBLE TO N. N. R.

The Herradora Intravenous Specialties of the Scientific Chemical Co. are inadmissable to New and Nonofficial Remedies for the following reasons:

1. The therapeutic claims advanced for them are unwarranted and exaggerated, and there is no evidence to warrant the intravenous administration of them.

2. With one exception ("Herradora's Sodium Iodid for Intravenous Use") the preparations are mixtures of drugs, the administration of which is not in the interest of sound therapy, particularly when these preparations are intended for intravenous use.

3. Herradora's Sodium Iodid for Intravenous Use is marketed with unwarranted therapeutic claims, such as:

"As prepared sterile by me, the sodium iodid molecule has been subjected to a process which renders it easier for the iodin atom to free itself in the tissues much more rapidly than in ordinary sodium iodid."

In reporting on Venodine,[6] a sodium iodid preparation, the Council held that, since iodids are easily absorbed from the mucous membrane of the gastro-intestinal tract and are usually well tolerated by the stomach, there is no reason for resorting to intravenous administration. This view the Council subsequently reiterated.[7]

4. With the exception of Herradora's Sodium Iodid, Calcium Compound, and Iodids Compound, all of the Herradora specialties are claimed to contain ingredients, the identity and the uniformity of which are not insured by their inclusion in the U. S. Pharmacopeia, National Formulary, or by their admission to New and Nonofficial Remedies. Were the Herradora preparations which contain such unstandardized

6. Articles Refused Recognition (Venodine; Standard Radium Solution for Intravenous Use), Report Council Pharm. & Chem., J. A. M. A. **64**: 2155 (June 26) 1915.

7. Some of Loeser's Intravenous Solutions, Report Council Pharm. & Chem., J. A. M. A. **76**: 1120 (April 16) 1921.

constituents acceptable otherwise, it would be necessary that these constituents be examined as to their composition, as to the methods employed to insure their identity and uniformity and to determine that these constituents were of therapeutic worth. The following are the unacceptable constituents which are contained in one or more of the Herradora mixtures: "Arsenic-Organic Compound" (if the Scientific Chemical Co. admitted that this is sodium cacodylate, then the firm would be required to substantiate the highly improbable claims of superiority), Ferric Dimethylarsenate,[8] "Arsenic-Mercuric-Organic Compound," Lithium Chlorid, "Guaiacol-Glyceryl Ester," "Digitalin" (the term is without meaning unless it is specified whethed "German," "French' 'or "True" is used), Convallamarin,[9] Adonidin, Nickel Bromid, Lithium Benzoate, Manganese Citrate, Manganese Glycerophosphate, Sodium Lactate and "Mercuric-Organic Compound."

The facts presented in the preceding report were sent the Scientific Chemical Co. In reply the company assured the Council that its "literature and compounds" were being changed "to conform to Handbook of Therapy American Medical Association" and requester further postponement of the consideration of its products.

FUNDAMENTALLY IRRATIONAL

The preparations of the Scientific Chemical Co. are fundamentally irrational and by no effort could they be made eligible for admission to New and Nonofficial Remedies. The Council, however, wished to give the company every opportunity to bring the preparations into conformity so far as possible with the rules that govern the Council in the consideration of articles, and for this reason the Council has postponed definite action for nearly a year.

Advertsing matter mailed to a physician in February, 1923, illustrates the methods followed by the Scientific Chemical Co. in the exploitation of its preparations. One of these circulars, entitled "Influenza and Pneumonia, Its Treatment" begins with a number of trite sayings, thus predisposing the reader to agree with its author. Then follows a rather bold statement that the author is not in accord with the manner in which the diseases are often treated and he proceeds to give details of the treatment of influenza and of pneumonia. The discussion contains much that is misleading if not definitely

8. Ferric Cacodylate Omitted from New and Nonofficial Remedies, 1920, p. 62.

9. Marvin, H. N., and White, Paul D.: Clinical Studies of Drugs of the "Digitalis Series," J. A. M. A. 77: 1865 (Dec. 10) 1921.

false. Thus the author speaks of coal-tar antipyretics being more or less hemolytic. It is true that they are capable of producing hemolysis when used in excessive doses but they are not dangerous when used properly.

It would be profitless to follow the maze of polypharmacy expounded in this circular through all of its ramifications. It suffices to illustrate the absurdity of the advice offered by stating that its author recommends a succession of twelve substances or mixtures containing a total of thirty-nine drugs in the treatment of influenza! A like number (including repetitions) are recommended for the treatment of pneumonia. Some of the preparations recommended contain no less than six different drugs, the combined action of which no human being can possibly foresee.

Not only does the circular recommend an extraordinary number of substances to be administered intravenously in these conditions, but it recommends many that, though once popular, have been shown to bt devoid of any therapeutic value in the treatment of any disease. An example of this is found in the recommendation of hypophosphites as represented by "Arsenic-Hypophosphite Compound."

Another circular is entitled "The Treatment of Arteriosclerosis and High Blood Pressure" with the subtitle "Arteriosclerotic Serum (Herradora) for Intramuscular Use." This begins with a discussion of the cause of arteriosclerosis followed by the recommendation that the condition be treated by the usual measures including restricted diet, by purgation and then with the "Herradora Serum." The latter is sometimes referred to as a solution and sometimes as a serum. It is admitted to be nothing more than a solution of the iodid, sulphate, phosphate and carbonate of sodium.

A perusal of the "literature" issued by the Scientific Chemical Co. leads to the belief that the firm is much more interested in persuading the unthinking to use its specialties than it is in scientific therapy. It is an affront to rational therapy to have these mixtures which are reminiscent of the old days of polypharmacy exploited in the treatment of such serious diseases as pneumonia and influenza. Medicine continues to have its disappointments with whatever therapeutic measures are followed in the treatment of pneumonia, which is one of the most baffling of diseases, but there is no possibility of progress while following such crude and unscientific measures as those advocated by the Scientific Chemical Company.

The Council is convinced that the propaganda contained in the advertising matter issued by the Scientific Chemical Co.

is detrimental to the rational practice of medicine and the public welfare. Therefore it has authorized publication of this report.

INTARVIN

Preliminary Report of the Council on Pharmacy and Chemistry

Because of numerous inquiries received, the Council has authorized publication of the following report.

W. A. PUCKNER, Secretary.

Intarvin is marketed by The Intarvin Co., Long Island City, New York. Dr. Max Kahn, Associate in Biochemistry, Columbia University, and physician in charge of metabolic diseases at Beth Israel Hospital, New York, applied for a patent on the product, not as a discovery per se or for the process of manufacture, but for the discovery of its use in diabetes.

Many statements have been given the lay press by those interested in the promotion of Intarvin for use in diabetes, but as yet no publication has appeared in the medical press except preliminary reports by Kahn.[1] Due to this lay publicity, the public and the profession have heard conflicting stories. Intarvin is hailed as lesser than insulin, and greater. Its severest critic says ". . . intarvin is neither new nor valuable." Some claim that it is easily tolerated; others that it has a "nauseating effect." The more conservative believe that it may prove valuable for use in diabetes.

Intarvin, recommended for use in diabetes or any condition wherein acidosis occurs, is the result of the application of a chemical theory to synthesize a fat with no potential danger for producing acidosis. In diabetes, in addition to the lack of assimilation of carbohydrates, there occurs incomplete oxidation of fats. Fats are the glyceryl esters of fatty acids and in nature, fatty acids invariably are compounds with an even number of carbon atoms. In the process of digestion, these fatty acids break down by the removal of two carbon atoms at each step. In health, the end products of this process are carbon dioxid and water. In the incomplete combustion occurring in diabetes, the final product in the breaking up of the fat is not a two carbon atom complex, but a four carbon

1. Proc. Soc. Exper. Biol & Med. **19**: 265, 1922; **21**: 31, 1923.

atom one, butyric acid, which oxidizes to oxybutyric acid and acetoacetic acid, the products present in most conditions of acidosis. The theory behind Intarvin is simple: If a palatable fat could be produced from a fatty acid, with an odd number of carbon atoms, the end product of combustion could not be the four carbon atom complex that is responsible for acidosis. Such fats were known to science, but commercial processes for production, and the use of the fats when synthesized, had never been successfully demonstrated. Accordingly, Intarvin was synthesized and is stated to be essentially the glyceryl ester of margaric acid (a seventeen carbon atom acid). The name signifies its intermediary position between the usual sixteen and eighteen carbon atom fatty acids that occur in nature. As the glyceryl ester of margaric acid is very stiff, Intarvin is said to be admixed with from ten to twelve per cent. of liquid petrolatum to render it of softer consistency.

Theoretically, one molecule of glyceryl margaric ester should yield two molecules of dextrose. Dr. Kahn reports that the "administration of this fat (Intarvin) to phlorhizinized dogs causes a marked increase in the glucose elimination in the urine, showing that *in the dog* it is broken down to propionic acid and is then converted to glucose. . . ." The antiketogenic effect would undoubtedly depend on the yield of dextrose and stipulate that the dextrose was burned in the body. Even if the available dextrose was not burned, but the remainder of the fat completely oxidized, a yield of approximately 7.7 calories per gram to the organism should result.

Diabetes, at the present time, has two established methods of treatment: (1) a carefully controlled diet, and (2) the administration of insulin in order that the patient may assimilate a maintenance diet. The discovery of insulin, which gives a means of enabling the diabetic person to assimilate not only carbohydrates, but natural fats, curtails the usefulness of Intarvin. Insulin treatment, however, is not without its disadvantages. The dose of the drug must be most carefully calculated and balanced against the diet; it must be given subcutaneously, often one, two or three times a day in the more severe cases. In view of these difficulties, an artificial fat that would be at once palatable, cheap and free from danger of causing acidosis, should be valuable in planning a diabetic diet.

Intarvin is still in the experimental stage, and it is unfortunate that so much newspaper notoriety has been given it. At present, no sure estimate of its worth can be made.

Experiments with it are being conducted by some of the leading physicians in this country, but no reports of this work are yet available. Until the cumulative evidence for its usefulness, palatability and practicability is available, it is best to suspend judgment. It will probably find a field of usefulness, but how broad is that field remains to be determined.

INTRAVENOUS THERAPY

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., May 5, 1923, p. 1331

For some years the Council has urged conservatism in the adoption of the intravenous method of administering drugs. It has been necessary to do this to offset the propaganda of proprietary firms that, for commercial purposes, feature the indiscriminate use of intravenous therapy. In order that the status of this form of drug administration might be presented to the profession and that it might be made clear under just what conditions the intravenous administration of drugs is warranted, the Council appointed a committee to study the subject and prepare a report for publication.

The report which follows was prepared by this committee and submitted to the Council. The Council has endorsed it and authorized its publication.

W. A. PUCKNER, Secretary.

The administration of drugs by the intravenous method is being extensively exploited by firms who are commercially interested in the sale of "intravenous specialties." Because of undue enthusiasm inculcated by advertising and publicity, and through lack of sound judgment, many physicians are employing it unwisely in conditions where this method of administration is not indicated. In addition to the broad general claims of superiority of intravenous injection over other methods of administration the following specific advantages are commonly urged in its favor:

1. That it affords precision of dosage.
2. That there is no irritation of the gastro-intestinal tract.
3. That the drug is not altered or destroyed in the gastro-intestinal tract.
4. That the drug enters the blood stream without loss of time.

There is a legitimate field for intravenous therapy. Nothing this Committee says on the subject in the report that follows is to be construed as a condemnation of the legitimate application of this method of administering drugs.

These alleged advantages in the routine administration of drugs are more apparent than real, and they will be considered in some detail, though not exhaustively.

1. Precision of Dosage: An accurate definition of the word "dose" is necessary before proceeding to a discussion of the subject, because a number of meanings have been given to the word, and one must avoid confusing *precision in weighing and measuring* a drug, with *precision of dosage* of that substance. A physician administers a drug in order to induce a given effect. Obviously it is his desire to give the exact amount necessary to induce that effect—no more and no less. That amount is the dose of the substance for that patient, under the circumstances obtaining at that moment, and evidently it is not necessarily the exact dose of the drug for any other patient, or for that patient under other possible circumstances.

Since the physician never knows the exact dose of a drug until he has obtained the results sought, he chooses an amount arbitrarily, which he knows to be a fraction of the true therapeutic dose, and he administers this fraction repeatedly until the desired effects are obtained, that is, until the total therapeutic dose has been administered. This fraction, the weight or volume of which can be determined with precision, has come to be called "the dose" of the drug, and precision of weighing and measuring the fraction has come to be confused with precision of dosage.

The oral administration of a drug permits of the administration of as many fractions of the dose as the circumstances demand, and these vary with the susceptibility of the patient, the urgency of the case, and the dangers of overdosage. The intravenous injection of a drug, however, owing to the limitations inseparable from this mode of administration practically makes it imperative to give the whole of the calculated therapeutic dose at once, except in the few cases which demand almost constant attendance by the physician. If this calculated dose proves insufficient, the patient suffers for want of the drug; if it happens to be more than the true therapeutic dose the patient suffers the toxic effects proportional to error in the estimate, and the effects of overdosage are more severe following intravenous injection than after oral administration.

Drugs are absorbed from the gastro-intestinal tract at somewhat variable rates, but there is a fair degree of uniformity of absorption for a given drug. On the other hand, different individuals show varying differences in their reactions to a given drug, that is, greater tolerance or resistance. There is a greater probability that the intravenous dose will be too large or too small, than that the patient will show an essential departure from the rule with reference to absorption from the gastro-intestinal tract.

It is generally recognized, for example, that there is a greater danger in the intravenous injection of strophanthin than there is in the oral administration of digitalis, and a number of deaths have followed the intravenous injection of the exact "calculated dose" of strophanthin. One is justified in administering strophanthin intravenously only when the exigencies of the case demand prompt relief, even though it involves some risk.

A further analogy: Anesthesia is maintained conveniently by dropping chloroform on to a face mask and permitting the patient to inhale the vapor, though there is no constant ratio between the amounts used and those taken into the blood stream. In other words, the dose of chloroform—that is the amount required to maintain the desired depth of anesthesia—is administered in almost innumerable fractions, though the anesthetist does not know the percentage of any of these fractions that is absorbed. This fractional dosage by inhalation is strictly comparable to fractional dosage by oral administration when strychnin or another drug is used.

2. That There is no Irritation of the Gastro-Intestinal Tract: Many drugs cause disturbances of the gastro-intestinal tract which are carelessly termed "irritation" though the action may be due to a reflex from another organ. An example is the nausea and vomiting induced by digitalis bodies through their direct action on the heart. It is obvious that the intravenous injection of such drugs does not cause less disturbance of the gastro-intestinal tract than their oral administration. Much of the true irritation of the large intestine following the administration of metallic salts, such as those of mercury, is caused during their excretion, and this also is largely independent of their mode of administration. Drugs that are directly irritant to the gastro-intestinal tract are usually irritant to the veins, the heart, and to other organs with which they come in contact in greater concentration after intravenous injection than after oral administration, hence, there are even greater objections to the intravenous injection of irritant drugs than to their oral administration.

3. That Intravenous Injection Prevents Alteration or Destruction of the Drug in the Gastro-Intestinal Tract: Nearly all drugs which are used for their systemic effects are absorbed fairly rapidly from the gastro-intestinal tract, and with a little judgment the physician can choose a drug which is absorbed promptly. The liver is far more active in the destruction of most drugs than is the gastro-intestinal tract, and drugs reach the liver quite as readily when injected intravenously as they do when given by mouth. The liver seldom takes all of a drug out of the blood which passes through it once, but this is usually taken up in small increments and slowly destroyed. There are, it is true, drugs such as epinephrin and arsphenamin that are not suited for oral administration. This is no argument, however, for administering, say, sodium iodid, intravenously, simply because epinephrin is destroyed in the stomach.

4. Drugs Act More Promptly after Intravenous Injection: This advantage in extreme cases does not admit of discussion, but it is obvious that it is not of the slightest importance in the treatment of chronic conditions, or with drugs such as mercurials, iron, and iodids, which induce their therapeutic effects slowly even when they are injected intravenously. It is a mere shibboleth as it is commonly used, which holds the attention of the unthinking through the frequency of its repetition.

This Committee would point out again that it has no desire to discredit the rational use of drugs by intravenous injection, but, on the contrary, it seeks to avoid the accidents and disappointments that must follow the abuse of a method which rightly employed may be a life-saving measure. With increasing knowledge of the technic of using drugs, with the development of pharmacology it seems probable that intravenous injections will be limited to even fewer classes of drugs than at present.

The Committee recommends that the Council (1) place itself on record as opposing the reckless and indiscriminate use of drugs by intravenous injection with its attendant dangers and increased needless expense to the patient, and, (2) recognize the legitimate life-saving nature of intravenous administration of drugs in extreme cases.

The Committee holds that the indiscriminate use of the intravenous method in cases in which it is not necessary is as reprehensible as it would be to jeopardize the life of the patient and subject him to the inconvenience and expense of an unnecessary major surgical operation.

IRIDINOL

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., Nov. 24, 1923, p. 1807

The Council has authorized publication of the following report. W. A. PUCKNER, Secretary.

About fifteen years ago, the idea occurred to nostrum manufacturers to exploit iridium as a medicament. "Iridium (Medicinal)" was put on the market by the Platinum Co. of America (THE JOURNAL A. M. A., April 23, 1910, p. 1389), and the same company manufactured "Iridinol," which was marketed by the P. H. Potter Chemical Co. (now P. H. Potter and Sons, Inc.), New York. Both products were, at that time, claimed to contain iridium and were marketed for a high price with grossly misleading therapeutic claims. Iridium (Medicinal) seems to have been abandoned, but Iridinol, advertised by P. H. Potter and Sons, Inc., as an "ethical preparation" continues to be sold to physicians as well as to the laity when occasion offers.

In the earliest advertising, Iridinol was claimed to be a "nontoxic preparation of iridium." At the time this claim was made, an examination made by the Chemical Laboratory of the A. M. A. revealed that the specimen contained iron, probably in the form of chlorid, and ammonium salts. Tests for iridium were negative. In view of the difficulty of detecting iridium, it is possible that traces of that metal may have been present, but the amount certainly was not very large. Regardless of the presence or absence of traces of iridium, there is not the slightest evidence for the therapeutic value of this metal in the conditions for which it is recommended by its exploiters. No reference to iridium can be found in such standard works on pharmacology as Sollman's, Cushny's, Meyer and Gottlieb's, Wood's and Bastedo's.

No longer in the printed advertising is a definite claim made for the presence of iridium in Iridinol. Instead the agents merely imply its presence as the following indefinite and meaningless statements show:

"Iridinol is a perfected aqueous solution of *one metallic element* [Italics ours], containing within itself a radiant energy not absolutely definable, but proved to be non-toxic in any amount given. . . ." and "This *6% solution of the metallic element* [Italics ours] represents 30 grains of the element to the ounce of aqua."

The claims for the use of Iridinol have also undergone a change. Specific statements of its curative value have become general. Among the early claims were:

"Cases of anemia respond promptly to its blood-building action, and cases of rheumatism of long standing and extreme degree, show almost startling improvement from the first dose. Tertiary forms or the sequelae of syphilis are cured."

Iridinol was formerly exploited as an antiseptic and curative agent in gonorrheal infections, and was recommended in typhoid fever, influenza and as a "systemic alterative and antiseptic of similar action to gold and mercury, but with the very important advantage that *it is absolutely free from toxic or deleterious effect.*" Today the advertising material can be classed in two groups, that printed and that written by the promoters to the prospective users of Iridinol. In the printed advertising, at least, the claims for the use of Iridinol are less specific than formerly. It is recommended in "anaemia," "rheumatism," "specific blood diseases," "diseases of the nose and throat," "of stomach organs," "liver and kidney," "of the nervous system," "diseases of children" "and as a systemic alterative." Such absurd claims are put forward as:

"Iridinol in its activities enters at once into the circulation, lowering the temperature, if too high, raising the temperature, if too low, in other words bringing it to normal. The same effect is noted on the pulse, bringing the pulse to normal, whether too low or too high."

The word "ethical" is used extensively in the Iridinol advertising in spite of the fact that, first, the preparation is of secret composition; second, the claims for the therapeutic value are not supported by any real evidence, and finally the methods of advertising are questionable. In one of the circulars, for instance, a quotation from "Rational Therapy" by Dr. Lerch of Tulane University is so used as to imply a recommendation by him for the use of Iridinol as a blood purifier, when, in reality, his statement is of the most general character and in no way connected with Iridinol. Again, in a letter written to a physician, Iridinol is recommended most strongly for the treatment of epilepsy. Further, there is evidence that the firm will sell Iridinol to the laity. A woman who wrote the firm regarding the product received in reply a letter which prescribed Iridinol for her only half-disclosed ailments and offered her the nostrum at $12 an ounce.

In view of the long-continued activities of P. H. Potter and Sons, Inc., in the promotion of Iridinol, the Council has authorized publication of this report for the information of physicians who may be importuned to use it.

JUNICOSAN NOT ACCEPTED FOR N. N. R.

Report of the Council on Pharmacy and Chemistry

The Council has authorized publication of the following report. W. A. PUCKNER, Secretary.

Junicosan is a potassium guaiacol-sulphonate preparation manufactured by Pharm. Chem. Fabrik., L. Lichtenheldt, Meuselbach, Germany. Hans P. Wesemann, New York, acts as U. S. distributor for the preparation.

According to the U. S. distributor the active ingredients of Junicosan are potassium guaiacol-sulphonate, 7 per cent., "Syrup. aromat. aurantiorum," 40 per cent., and "Junipur (Extr. junip. puriss)," 53 per cent. The distributor states that to obtain "Junipur," "Extr. junip." is made "in the usual manner, but this extract is then freed from all inert and inactive matter and concentrated about 10 times in a vacuum." No information was furnished the Council in regard to the composition of Junipur and of the method of its manufacture; therefore, Junipur and Junicosan (which is stated to contain junipur as its principal ingredient) are of essentially secret composition.

On the label of Junicosan (which is in German) it is claimed that the preparation is used with success in all diseases of the respiratory organs and that at the same time it is a superior stomachic. A circular (in German) which is wrapped with the trade package contains the assertion that Junicosan is recommended by physicians, that it has long been tried and has always given good results in affections of the air passages and respiratory organs and that it is employed with favorable results in all catarrhal, especially chronic affections, as bronchial and pulmonary catarrh, cough, whooping cough, and in convalescence after pneumonia, influenza, etc. It is further asserted that the preparation is used with especially good results in all stages of tuberculosis. These extravagant claims are likely to lead to the indiscriminate and ill-advised use of this proprietary mixture by the public; and, moreover, they are quite unwarranted. As a matter of fact, potassium guaiacol-sulphonate has been claimed to be of some value as an expectorant in the treatment of pulmonary disease and incipient tuberculosis, but it has not come into general use. There is no evidence that any preparation of juniper is of value in the treatment of the diseases for which Junicosan is exploited. The aromatic syrup of orange is a flavor only.

The Council declares Junicosan inadmissible to New and Nonofficial Remedies (1) because its composition is indefinite

(Rule 1); (2) because it is exploited with unwarranted therapeutic claims and in a way to lead to its ill advised use by the public (Rules 4 and 6); and (3) because it is an irrational combination marketed under a noninformative name (Rules 8 and 10).

LACTIC ACID-PRODUCING ORGANISMS AND PREPARATIONS

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., Sept. 8, 1923, p. 831

The Council has authorized publication of the following report. W. A. PUCKNER, Secretary.

Milk soured by acid-producing organisms which are more or less natural to ordinary commercial milk, or by certain types or species which are intentionally added with or without the association of alcohol-producing yeasts (kefir, kumyss), has been used as a food for centuries. This more or less extensive practice is due to the fact that the products were palatable to many, or rested on the assumption among the laity, as well as physicians, that they were beneficial in the correction of certain disorders of the gastro-intestinal tract. A great stimulus to the employment of fermented milks was given by the theories of Metchnikoff regarding intestinal putrefaction. These theories were in part that if the products of so-called "intestinal putrefaction," elaborated chiefly in the large intestine, were absorbed, by their action on the walls of the blood vessels they produced arteriosclerosis and premature senility. He also advanced the theory that the growth of the proteolytic bacteria which elaborated these poisons could be modified or prevented by the presence in the intestines of lactic acid-producing bacteria. For this purpose he advocated the use of *Bacillus bulgaricus.*

During recent years, reports have been published from different laboratories which indicate that the growth in the intestinal canal of the normally present *Bacillus acidophilus* may be increased so as to make it the predominating organism, by the administration of lactose (sugar of milk), by milk inoculated and fermented with *Bacillus acidophilus,* or by the administration of viable cultures of *Bacillus acidophilus* in conjunction with lactose. Growing out of the claims of favorable therapeutic action which are based on more or less extensive experimental data, the use of so-called Bacillus acidophilus milk and other products prepared with *B. aci-*

dophilus has become quite widespread in this country. While no one subscribes seriously today to the original theories of Metchnikoff, there are many who believe that the regulation of types of bacteria and of the bacterial activities in the intestine is of much importance from the health standpoint. Since *B. acidophilus* and its very close neighbor, *B. bifidus,* are very common and as a rule the predominating types in the intestines of breast-fed infants, and furthermore, since extensive experiments have been made which show these organisms to be of a strictly nonputrefactive and apparently harmless nature, added weight is given by many to the claims made as to actual therapeutic value.

There is evidence that the administration of sour milk is at times beneficial. This is particularly true in pediatrics, in which field fermented milks have found a wide application. Sour milk and sour milk products are used in cases of vomiting, and of acute diarrhea, as well as in chronic disturbances of the gastro-intestinal tract. On what the particular value of sour milks as such depends is not known at the present time. There can be no doubt that a wide clinical observation gives a basis for the opinion that, for certain types of gastric and intestinal disturbance, fermented milk accomplishes more than sweet milk with a similar fat, sugar and protein content. No one will, of course, deny the great value of milk as a growth-producing and energy-yielding food, whether the milk is sweet or whether it is soured by any of the so-called "lactic acid bacteria."

Recent observations made at various laboratories seem to indicate that, in contrast with *B. acidophilus, B. bulgaricus* cannot be implanted or made to proliferate in the intestine, even when administered in large numbers. Much doubt is cast, therefore, on any alleged physiologic action that this organism was claimed to have in the intestine. It is for this reason, and because *B. acidophilus,* according to numerous reports, can be successfully implanted, that preference is now given by many in the use of lactic acid bacillus cultures to those prepared with *B. acidophilus.*

There is little, if indeed any, satisfactory proof that liquid cultures or aqueous suspensions of lactic acid-producing organisms are of real value as local applications to mucous membranes or in arresting putrefaction or suppuration in wounds, abscesses and sinuses. In such conditions, their use appears to be still in the experimental stage.

Sour or fermented milk may be administered in the form of buttermilk or naturally soured skim milk, the lactic acid being produced by *Streptococcus lacticus,* which occurs commonly in milk and other dairy products and grows readily at ordi-

nary room temperature; also in the form of sour milk produced by *Bacillus bulgaricus*.

To these may be now added the so-called Bacillus acidophilus milk which is prepared by the inoculation of milk which has been previously sterilized or heated for about an hour, at or near boiling temperature, with a pure starter made by inoculating pressure-sterilized milk with viable *B. acidophilus* and incubating at from 35 to 37 C. for from twenty to twenty-four hours. On the completion of proper ripening, which should take place within from twenty to twenty-four hours at from 35 to 37 C., a product is obtained which is slightly sour to the taste and has a characteristic odor not very unlike ordinary pure buttermilk. There is a slight separation of whey, but, on thoroughly mixing, the product has a uniform creamy consistency. Bacillus acidophilus milk is produced in various laboratories and dairies, though in many instances with partial success only. It may be made from fresh skim milk, whole milk, or from skim milk to which varying amounts of cream have been added. In all milk culture work, mass inoculation with the use of a sterile pipet is necessary. The preparation of uniform pure Bacillus acidophilus milk requires adequate facilities, the aid of a trained technician, and close adherence to instructions.

Bacillus acidophilus and *Bacillus bulgaricus* belong to a group of bacteria, the lactobacillus group, which has not until recently received much scientific attention, but which is widely distributed in nature. Both are long and fairly slender bacilli, which at times have a tendency to filament formation. They are preferably micro-aerophilic, but grow well under ordinary aerobic conditions. They are gram-positive, though in old cultures individual rods or filaments may at times fail to retain the stain. In spite of claims to the contrary, branching may be observed only occasionally, the branched forms resembling more or less another organism of this group, *Bacillus bifidus*, which quite commonly reveals branching.

Both organisms require carbohydrates for their successful cultivation. Glucose, galactose and lactose broth are fairly suitable, but much less favorable than milk or milk whey. Milk is a particularly good medium for the preservation of viability. For isolation purposes and for colony study, whey-agar and galactose or lactose agar may be used to advantage.

Bacillus acidophilus and *Bacillus bulgaricus* have very many points in common. They differ, however, in the following respects: 1. *B. acidophilus* is relatively slow in acid production in milk, the amount of acid produced during twenty-four hours' incubation rarely exceeding 1 per cent., whereas milk cultures of *B. bulgaricus* may attain an acidity of 3 per cent. in the same period of time. 2. Except in the case of so-called border strains, *B. acidophilus* attacks maltose with acid production, while *B. bulgaricus* is unable to do so. 3. *B. acidophilus* is of intestinal origin and, therefore, can adapt itself to intestinal conditions, whereas *B. bulgaricus* is an ordinary saprophyte and is unable to develop or even to maintain itself in the digestive tract.

The group of lactobacilli is probably one large group which consists of many varieties, in the same way as the *B. coli* and the streptococcus groups. Certain members of the lactobacillus group (acidophilus and bifidus types) are found in the feces of man and animals. Others

(bulgaricus type) are very common in cow barns and in dairies, and in the various dairy products. The well-known *Bacillus bulgaricus* is the predominating organism in the oriental sour milk products, and it is to this type of the lactobacillus group that these products in a large measure owe their characteristic properties. All cultures of *B. acidophilus* and *B. bulgaricus* deteriorate with age, and, therefore, should be used soon after they are prepared. While viability appears to be preserved best in milk cultures, even these should have a brief expiration limit, and should be kept at relatively low temperature. Experience has shown that *B. bulgaricus* and *B. acidophilus* are short-lived in so-called tablets and powders. Bacteriologic examination of such powders and tablets, and of various broth cultures, has often shown them to contain, at the most, but few living aciduric organisms. All lactic-acid ferment preparations should be kept at or near ice-chest temperature and marked with an expiration date.

MAMMARY SUBSTANCE DESICCATED-WILSON NOT ACCEPTED FOR N. N. R.

Report of the Council on Pharmacy and Chemistry

The Council has authorized publication of the following statement.

W. A. PUCKNER, Secretary.

The Wilson Laboratories market Mammary Substance Desiccated, Mammary Substance Tablet 2 grs. and Mammary Substance Tablet 5 grs. In view of the slight evidence for the therapeutic value of mammary gland preparations which has accumulated during the many years of their trial, the Council voted to omit all mammary gland preparations from New and Nonofficial Remedies, 1922. In consideration of this action, the Council voted not to accept the product of the Wilson Laboratories.

MERCURIAL OIL OMITTED FROM N. N. R.

Report of the Council on Pharmacy and Chemistry

The Council has authorized publication of the following report.

W. A. PUCKNER, Secretary.

Mercurial oil—also called grey oil—is finely divided metallic mercury in a liquid, oily suspension. The product is described in New and Nonofficial Remedies, 1922.

Mercurial oil is used by intramuscular injection as a means of obtaining the systemic effects of mercury. New and Nonofficial Remedies contains the caution that, according to reports, cumulative effects are prone to develop from its use, and, in view of the report by Cole, Lipmann and Sollmann (The Journal A. M. A., Dec. 4, 1920, p. 1559), the statement that according to a recent study of the absorption of mercury

preparations (administered intramuscularly) mercurial oil injections are both inefficient and dangerous.

The Council has become convinced that mercurial oil is a menace and that equally good results can be obtained without it; and that the retention of mercurial oil in the practice of syphilology will cause unnecessary harm in some instances. Since the retention of mercurial oil in New and Nonofficial Remedies may be conducive to its retention in therapeutic practice, the Council decided to omit the preparation from the book.

NEISSER-SAN-KAHN NOT ACCEPTED FOR N. N. R.

Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., Jan. 20, 1923, p. 201

The Council has authorized publication of the following report.

W. A. PUCKNER, Secretary.

Neisser-San-Kahn is marketed by the York Laboratories, York, Pa., as "a new genito-urinary product" with the claim that, "in Neisser-San-Kahn the genito-urinary surgeon has at his command a new salt of marked value in urethral infections." The product is said to be a definite chemical body, zinc borosalicylate, and to have the composition indicated by the chemical formula "$(C_{14}H_{10}BO_7)2Zn$." The following statement with reference to the method of manufacture was furnished the Council:

"PREPARATION. Boric-acid being converted into hydrogen Tetraborate $H_2B_4O_7$. With a certain amount of Acid Salicylic and Zincum Carbonatum, (Normal) it forms the body of the product through crystallization. The crystals are recrystallized from hot water to discard the irritating property of the Acidum Salicylicum."

Neisser-San-Kahn is claimed to be "especially adapted for treatment of all forms of Neisserian infection." The preparation is marketed in the form of tablets. A blotter, evidently intended for the druggist, advises:

"In the absence of other instructions from the prescribing physician, Neisser-San-Kahn should be dispensed as follows: 1 tablet (1 gm.) Neisser-San-Kahn in three (3) ounces hot distilled water."

Although Neisser-San-Kahn is said to be a new chemical compound, a preparation claimed to be zinc borosalicylate was introduced about ten years ago (in Germany) with claims similar to those now advanced for Neisser-San-Kahn. This German preparation was called Dr. A. Foelsing's

"Mucosan." Mucosan was analyzed at the University of Giessen by K. Feist (*Apotheker Zeitung,* 1912, p. 306). Feist concluded that the product presented a loose chemical combination of zinc salicylate, salicylic acid and boric acid, and that a product having properties identical with those of Mucosan is obtained when a mixture of boric acid 2.11 gm., zinc salicylate (hydrated) 5.63 gm. and salicylic acid 2.86 gm. is dissolved in a little water and the solution evaporated to dryness.

As evidence for the therapeutic value of Neisser-San-Kahn the York Laboratories submitted letters from physicians who had used the preparation. These did not indicate that the preparation has any other action in urethritis than that of zinc sulphate. Zinc sulphate is indicated only in certain forms of urethritis and the submitted evidence presented no warrant for the general use of the preparation advocated by the firm which markets it. The market is crowded with preparations proposed for the treatment of urethritis and the combination presented in Neisser-San-Kahn appears to have no advantage over established drugs.

The Council declared Neisser-San-Kahn inadmissible to New and Nonofficial Remedies on the following grounds:

1. It is an unoriginal preparation marketed under a proprietary, nondescriptive name. The rules of the Council provide that a proprietary name for a medicinal article shall be recognized only when the use of such an exclusive name is in the interest of the public welfare. In consideration of the benefits which may come from the discovery of a therapeutic agent the Council concedes to the person or firm which, by right of discovery, controls such a product the right to name it and offers no opposition to an arbitrary name for such a product. The combination presented by Neisser-San-Kahn and claimed to be zinc borosalicylate, however, is not the discovery of the York Laboratories and hence the Council cannot recognize the proprietary and nondescriptive name of this firm.

2. The therapeutic claims are not substantiated by acceptable evidence and are, therefore, unwarranted.

3. The available evidence fails to show that the preparation, claimed to be zinc borosalicylate, has any advantage over established zinc salts. The use of substances which are unessential modifications of established drugs is unscientific and serves no useful purpose and hence, in the absence of evidence of superiority over established zinc salts the use of this so-called zinc borosalicylate is not in the interest of rational therapy.

PEPTONE IN THE TREATMENT OF MIGRAINE

Preliminary Report of the Council on Pharmacy and Chemistry

From The Journal A. M. A., June 30, 1923, p. 1910

The Council has authorized publication of the following statement on the experimental status of Peptone in the treatment of migraine. W. A. PUCKNER, Secretary.

Drs. Joseph L. Miller and B. O. Raulston report on the effects produced by the intravenous administration of Peptonum Siccum-Armour in the treatment of migraine.[1] The authors report that twenty-five patients have been under observation for a sufficient period of time to permit conclusions to be drawn in regard to the results of the treatment. Of these patients, nine were much improved in that they were free from headache for two months or longer after the treatment was discontinued. When the headache returned, it was again controlled by the administration of Peptonum Siccum-Armour. Expressed in percentages, 36 per cent. were much improved; 48 per cent. were moderately improved, and 16 per cent. were not benefited. The authors report that in several hundred injections, they have never observed any symptoms resembling anaphylactic shock. Another physician, however, has observed marked urticaria following a single injection of peptone in two cases, and the opinion is expressed that different preparations may differ in composition.

Commercial peptones are heterogeneous mixtures of uncertain composition. No adequate tests and standards have been developed whereby the uniformity of a given brand of peptone may be controlled, and it is probable that different lots differ in composition. The results that are reported from the use of the peptone used by Miller and Raulston may have been due to tissue impurities rather than chemical peptone itself. It is evident, therefore, that the reported results cannot be made the basis for a rational treatment of migraine. However, if physicians decide to carry out controlled experiments along the lines indicated, it is most important that the identity of the peptone which is used be determined as far as possible.

The peptone preparation used by Miller and Raulston in their clinical study was Peptonum Siccum-Armour, manufactured by Armour & Co., Chicago. This product is stated

1. Miller, J. L., and Raulston, B. O.: Treatment of Migraine with Peptone, this issue, p. 1894.

to contain 90 per cent. proteins. Seventy per cent. of the protein content is stated to be in the form of peptone and secondary proteoses, while the remaining 30 per cent. is in the form of amino-acids. Those who wish to confirm the report of Miller and Raulston should use the particular product used by them or one which has essentially similar composition.

PERTUSSIS BACTERIN MIXED (MULFORD) AND PERTUSSIS SEROBACTERIN MIXED (MULFORD) NOT ADMITTED TO N. N. R.

Report of the Council on Pharmacy and Chemistry

The Council has authorized publication of the following report. W. A. PUCKNER, Secretary.

The H. K. Mulford Co. markets Pertussis Bacterin Mixed and Pertussis Serobacterin Mixed. These preparations are stated to contain the following organisms: pertussis bacillius, influenza bacillus, staphylococcus aureus, staphylococcus albus, streptococcus pneumococcus (types I, II and III) micrococcus catarrhalis.

In requesting the acceptance of these "mixed" vaccines for New and Nonofficial Remedies, the H. K. Mulford Company presented no evidence for the value of this complex mixture of organisms except a statement in the advertising circular for Pertussis Serobacterin Mixed that Appel and Bloom (*Arch. Pediat.*, March, 1922) in their report of the prophylaxis and treatment of pertussis used "a mixed sensitized pertussis bacterin." This report contains nothing to indicate that the results were more favorable than have often been reported from the use of the single pertussis bacillus vaccine.

It is stated in New and Nonofficial Remedies, 1922, for pertussis bacillus vaccine: The evidence indicating that it is of value both for prevention and treatment is very questionable, and the reports are conflicting. In the series of articles on biologic therapy prepared under the auspices of the Council on Pharmacy and Chemistry, Wilburt C. Davison (The Journal A. M. A., Jan. 22, 1921) concluded his discussion of the evidence for the value of pertussis bacillus vaccine: In summing up the prolific and somewhat contradictory literature of this subject, it may be concluded that injections of Bordet-Gengou bacillus vaccines may have a slight though unreliable prophylactic effect, and that therapeutic inoculations are of practically no value. Further

experiments are necessary to remove this procedure from the limbo of nonspecific therapy. In consideration of the questionable efficiency of the simple pertussis bacillus vaccine, the use of complex mixtures such as those of the Mulford Company are irrational and a detriment to rational therapy.

The Council holds that there is no evidence for the value of Pertussis Bacterin Mixed (Mulford) and Pertussis Serobacterin Mixed (Mulford) and declares these preparations inadmissible to New and Nonofficial Remedies because their use is illogical (Rule 10).

PHYLLOSAN NOT ADMITTED TO N. N. R.

Report of the Council on Pharmacy and Chemistry

On July 19, 1921, Merck and Co., New York, were informed that because of inquiries received, the referee in charge of iron preparations desired to determine the acceptability of "Phyllosan" for New and Nonofficial Remedies and invited the firm to submit the information required to determine the acceptability of the product. Merck and Co. replied that they were the purveyors only and that the request for information had been referred to the manufacturer, Swiss Serum and Vaccine Institute, Berne, Switzerland. At the expiration of three months no information had been received from Merck and Co. or the Swiss manufacturer and hence the referee based his examination of Phyllosan on the available literature and the advertising issued by Merck and Co.

The following report of the referee which declares Phyllosan inadmissible to New and Nonofficial Remedies because its composition is indefinite (Rule 1) and the Therapeutic claims unwarranted (Rule 6) was adopted by the Council and authorized for publication.

W. A. PUCKNER, Secretary.

Phyllosan, advertised and marketed by Merck and Co., New York, is manufactured by the Swiss Serum and Vaccine Institute, Berne, Switzerland. It is stated that the preparation is sold as Chlorosan in Switzerland and as Foliosan in England.

According to Merck and Co., Phyllosan "is a preparation of chlorophyll with certain derivative pyrrol bodies and iron" marketed in the form of tablets "each containing 0.03 gm. of the specially prepared chlorophyll and 0.005 gm. of iron in the form of a double phosphate."

The literature which bears on the virtue of the preparation which Merck and Co. market as "Phyllosan" apparently is

inspired by Professor E. Buergi, Director of the Pharmacologic Institute of the University at Berne, who recently originated the product (*Therap. Monatschr.* **32**:1, 1918, *Biochem. Ztschr.* **98**:256, 1919; C. F. Troczewiski, *Revue Suisse de Med.*, Oct. 7, 1916; R. Gregoriew, *Biochem. Ztschr.* **98**:284, 1919). From the articles in the *Therapeutische Monatshefte* and *Biochemische Zeitschrift* which the referee has read, evidence is presented in the form of experiments on rabbits made anaemic by bleedings and injections of phenylhydrazin. The animals were divided into four groups, (1) no medication, (2) iron alone, (3) chlorophyll alone, (4) iron and chlorophyll in the form of Phyllosan. From the protocols given, the regeneration of the hemoglobin and erythrocytes takes place most rapidly when Phyllosan is administered. Iron is present in small amounts, but is considered as an activator of the chlorophyll action. The results appear to be better with the combination of iron and chlorophyll than with either alone. The average return to normal without treatment is about five weeks; with Phyllosan it is about three weeks. The protocols of human cases are rather sketchy, no note as to diet being made, and are interpreted as favoring Phyllosan as a very useful agent in the treatment of chlorosis and secondary anaemia. A wide variety of cases is given: chlorosis, secondary anaemia from gastric ulcer hemorrhage, pulmonary hemorrhage in cases of pulmonary tuberculosis, debility, etc. Claims are made for its beneficial effect in cardiac disease and as a laxative, none of which are well supported by evidence.

The advertising issued by Merck and Co. is, on the whole, not extravagant. Phyllosan is presented as being used in "anaemia, chlorosis and wasting diseases." The claim, however, that it "improves the appetite" and that its "tonic effect is most helpful in hastening convalescence" and that it "exerts a beneficial influence in restoring to normal the cardiac action" cannot be accepted.

The referee feels that there is little to be accomplished in a therapeutic way by Phyllosan that cannot be gained by a good diet of meat, eggs, milk and fresh vegetables.

Phyllosan is inadmissible to New and Nonofficial Remedies because its composition is semisecret in that the amount of and character of the pyrrol compound contained in the product, the composition of the "double phosphate" of iron and the character of the "specially prepared chlorophyll" is not declared and because the therapeutic claims are not substantiated by acceptable evidence, and are, therefore, exaggerated and unwarranted.

The report on Phyllosan was sent to Merck and Co. In reply Merck and Co. stated that the "Pyrrol bodies" in Phyllosan "are not as yet very well understood"—"Perhaps they are antecedents of Chlorophyll in the chemical processes occurring in the plant during the production of Chlorophyll"—"At any rate they are extracted from the plant with the Chlorophyll." In reference to the double phosphate of iron, the firm states "we are now advised that a pyrophosphate of iron is present in the preparation." As to its composition, very little further information was furnished. The admission was made that essentially Phyllosan is nothing more than a plant extractive to which "a pyrophosphate of iron" has been added. The quantity of iron in a given quantity of Phyllosan was originally stated as 0.005 gm. in each tablet. Presumably, this quantity has not been changed. The substance referred to as "pyrrol bodies" are admitted to be merely components of the plant extractive.

The firm stated further, "As to the character of the specially prepared Chlorophyll to which you refer, perhaps the above is sufficient, but it may be added by way of enlargement that from the outset it has been the purpose not to try to prepare a pure Chlorophyll (on account of low medicinal value, expense, etc.), but to prepare a chlorophyllic extract of green leaves. Suitable solvents, and appropriate manufacturing limitations are employed so that a cell extraction of more than usual completeness is effected. On this account, the pyrrol bodies are in the extractive. No doubt, also, the lipoids, cell phosphatids (such as lecithin), and vitamins."

Merck and Co. wrote: "With regard to the action of Phyllosan on the appetite, in convalescence, and on the heart the manufacturers feel that these points are covered in medical literature submitted herewith." The "literature" consisted of reprints from Swiss and German medical journals. These contain nothing which permitted a revision of the criticisms regarding the lack of evidence for the therapeutic value of Phyllosan. On the other hand, the publications of Loeffler (*Cor.-Bl. f. schweiz. Aerzte.* **48**:1521, 1918; **48**:1618, 1918; **49**:879, 1919) are to the effect that Phyllosan gave negative results in extensive pharmacological and clinical tests. Loeffler found that Phyllosan was inferior to Blaud's pills in the treatment of anaemia, both in laboratory and clinical tests; he considered that there was no certain evidence that chlorophyll had any therapeutic action and he argued that even if chlorophyll had a therapeutic action it was unlikely that the minute amounts present in Phyllosan would be effective.

After considering the further information from Merck and Co., the Council concluded that the statement bearing on the composition of Phyllosan is still indefinite and that the therapeutic claims still lack substantiation by acceptable evidence, and, therefore, the Council reaffirmed its decision that Phyllosan be not admitted to New and Nonofficial Remedies.

PROGRESS AND CONSERVATISM IN THERAPEUTICS

A Report of the Committee on Therapeutics of the Council on Pharmacy and Chemistry

From The Journal A. M. A., June 2, 1923, p. 1635

The Committee on Therapeutics of the Council on Pharmacy and Chemistry of the American Medical Association prepared the communication which appears below for the purpose of calling to the attention of physicians two books, published by the Council, which are of great value to all who are actively engaged in the practice of medicine.

W. A. PUCKNER, Secretary.

We, the undersigned, constituting the Committee on Therapeutics of the Council on Pharmacy and Chemistry of the American Medical Association desire to call to the attention of physicians the two books "New and Nonofficial Remedies" and "Useful Drugs." For eighteen years the Council has done its utmost to bring before the medical profession the truth concerning the new proprietary medicinal preparations which are being offered to the profession.

In addition to its permanent secretary and the editor of THE JOURNAL of the American Medical Association, the Council consists of a group of clinians, pharmacologists and chemists appointed by the Board of Trustees of the American Medical Association, because of their individual fitness to investigate the problems of drug therapy. The purpose of the Council is to disseminate the truth in matters pertaining to the use of drugs and thereby improve drug therapy. In this connection it has been operating a chemical laboratory in charge of the permanent secretary and manned by a personnel especially trained in the field of drug analysis. In addition, through its committee on therapeutic research, it has fostered and financed many investigations in the fields of pharmacology and therapy.

While, as stated above, the Council was organized primarily to put a stop to the exploitation of proprietary medicines

under false claims and to the use of secret preparations, its activities have broadened until its work may now be characterized as "a propaganda for the rational use of drugs." Evidence of this broader policy is seen in the publication of these two books.

NEW AND NONOFFICIAL REMEDIES

In New and Nonofficial Remedies are listed and described such new preparations as, in the opinion of the Council, give promise of being more or less value in the practice of medicine and are ethically presented to the medical profession. While many of the preparations described in the book are on trial, and no doubt will ultimately be discontinued or replaced by better products, a considerable proportion of the preparations are of unquestionable value and in the course of time will be found to be permanent and necessary aquisitions to our therapeutic resources.

The acceptance of a preparation for New and Nonofficial Remedies is governed by a set of rules formulated by the Council. The rules require in effect that the quantitative composition of the product be declared; that no undue or grossly exaggerated therapeutic claim be made for it; that the method of exploitation shall not be contrary to the best interests of the public and the medical profession, and that it should possess or give promise of having therapeutic value. Acceptance by the Council carries with it admission to the advertising columns of the Association's Journals, while rejection debars the product from such privileges.

New and Nonofficial Remedies constitutes a ready reference book in which can be found the description of new preparations of an ethical character, their composition, indications and uses and the dosage to be employed. Opinions of the Council also appear, expressed in the discussion of the various classes of remedies. This opinion should be worthy of consideration since it is based on a thorough study of the drug in question and is expressed with frankness. In cases in which physicians should be put more than usually on guard in the use of a given article reference is made to any question that impresses itself on the Council in connection with the history or probable outlook for any preparation.

The Council is so constituted that cooperation enables it to investigate the literature as no individual could possibly do. The secretary with the cooperation of the editorial staff of THE JOURNAL assists the individual members by securing the necessary literature, and by references to reports which have been made on proprietary articles in the past. This is important, for these proprietary preparations go through

stages of development, and thus a clear estimate of the value of drugs may be found in the book. The book is revised yearly. Those products which fail to live up to expectation or to the claims of the proprietors are omitted, while new ethical preparations meeting the requirements of the Council are added. Therefore the book represents the current opinion of the Council. It is the ambition of the Council that New and Nonofficial Remedies shall become the accepted guide for physicians in the recognition of new remedies.

USEFUL DRUGS

In order to improve the instruction in medical schools in pharmacology and materia medica and to aid the practicing physician in the choice of remedial agents, the Council has selected a list of drugs which is the basis of the book "Useful Drugs," which is now the guide for the selection of drugs for instruction in many medical schools. Many state licensing boards confine their questions in pharmacology, materia medica and therapeutics to the drugs therein listed.

This book, also, undergoes frequent revision, taking into account the recent important advances in pharmacology and therapeutics. The needs of the practicing physician are kept in mind and the book should prove of special value both in the practice of medicine and in the teaching of pharmacology and therapeutics.

"Useful Drugs" and "New and Nonofficial Remedies"[1] together furnish information concerning all drugs, old and new, which are at present essential to, or give promise of value in, the practice of medicine. They have been compiled with a special object in view, namely, to meet the needs of the student and practitioner of today.

Respectfully submitted,

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SOMNACETIN AND SOMNACETIN SOLUBLE NOT ACCEPTED FOR N. N. R.

Report of the Council on Pharmacy and Chemistry

The Council has authorized publication of the following statement. W. A. PUCKNER, Secretary.

Somnacetin and Somnacetin Soluble are products of the firm Drs. R. and O. Weil, Frankfurt-on-Main, Germany. They are sold in the United States by Reidar G. Seel, New York.

Somnacetin is marketed in the form of tablets. Each tablet is stated to contain "sodium diethylbarbituric acid-acetphenetidin 4.6 gr., codein phosphate-Weil 0.2 gr." No evidence is offered to show that Somnacetin tablets contain a chemical compound "sodium diethylbarbituric acid-acetphenetidin," nor is there a declaration of the amount of sodium diethylbarbituric acid (barbital sodium) and acetphenetidin represented by each tablet. In 1912 the Council considered a product of Drs. R. and O. Weil which was called Veronacetin marketed in the form of tablets claimed to contain a mixture of barbital sodium, acetphenetidin and codein phosphate. This was not accepted. In 1915 the Council was asked to consider what appeared to be essentially the same product, but which was now called Somnacetin and claimed to contain a definite chemical compound of acetphenetidin and codein with diethylbarbituric acid (barbital). This was not accepted.

Somnacetin Soluble is a liquid sold in ampules. Each ampule is declared to cantain "6 gr. sodium diethylbarbituric acid, 3.5 gr. Pyrazol, 0.015 gr. codein phosph.-Weil." Pyrazol is a well known chemical substance, but it is not used in medicine. From publications in German medical journals it is probable that the "pyrazol" of Somnacetin Soluble is antipyrine, the chemical name of which is phenyldimethylpyrazolon.

According to the advertising of Reidar G. Seel, Somnacetin is a hyponotic, sedative and anodyne which is "indicated particularly in insomnia due to excitement, anxiety or depression, pain or to pathologic conditions such as accompany myocarditis, arteriosclerosis, Basedow's disease, gastrointestinal disturbances, etc." It is also claimed to be useful when given preliminary to general anesthesia and is claimed to be "a valuable adjuvant in the so-called 'Twilight Sleep'" and "may also be employed as a prophylactic in car-sickness

and sea-sickness." Somnacetin is also advised "as Anodyne in rheumatic conditions . . . to be alternated with the antirheumatic or other medicament."

Somnacetin Soluble, according to the advertising, is suitable for subcutaneous, intramuscular and rectal administration. Its use is proposed in insomnia and gastro-intestinal disturbances.

In 1911 von Noorden proposed in a short note (*Therap. D. Gegenw.* **52**:287, 1911) a mixture of 0.3 gm. barbital, 0.52 gm. acetphenetidin and 0.025 to 0.03 gm. codein and stated that this dose was equal to 0.6 gm. barbital without the side actions of the latter. He gave no evidence, however, in support of his statement. In 1919 von Noorden (*Therap. Monatshefte,* **33**:413) reported experiments with mixtures of sulphonmethan, sulphonethylmethan, acetphenetidin, antipyrin and other drugs. He came to the conclusion that none of the mixtures were as satisfactory as the mixture first proposed by him. Von Noorden stated that his mixture had no advantage over barbital when administered per rectum. To provide a soluble form, a solution containing 20 per cent. of barbital sodium, a "corresponding quantity" of antipyrin and 0.1 per cent. of codein phosphate "with minimal addition of an indifferent solubility-increasing nonprotein colloid" ("unter minimalem Zusatz. eines indifferenten, die Loslichkeit steigernden Nicht-Eiweibkolloids") was made. Von Noorden recommended the new preparation in a great variety of complaints, but submits no evidence that he has compared it with the separate constituents. M. Baer (*München. med. Wchnschr.,* 1912, No. 9), O. Mokenmoller (*Psych. Neurol. Wchnschr.* 14, No. 48, 1913) and S. Lowenstein (*München. med Wchnschr.,* 1914, No. 21, p. 1206) also have reported it to be useful and lacking side actions without having compared the effects with those of the separate constituents.

There is no evidence that the preparation marketed as Somnacetin has any advantage over a mixture of barbital sodium, acetphenetidin and codein. Further, there is no evidence to show that the preparation now marketed as Somnacetin has the actions of the mixture of barbital, acetphenetidin and codein reported by von Noorden, nor that the product Somnacetin Soluble has the actions of the solution of barbital sodium, antipyrin and codein phosphate devised by von Noorden. The Council declares Somnacetin and Somnacetin Soluble inadmissible to New and Nonofficial Remedies because (1) the composition of these preparations is not definitely declared and they are, therefore, essentially secret (Rule 1);

(2) the names of these preparations are not descriptive of their composition and the use of similar terms for preparations of essentially different mixtures is objectionable (Rule 8); (3) the use of fixed formula preparations representing barbital,, acetphenetidin (or antipyrin) and codein—particularly when marketed under noninforming names—will lead to their indiscriminate and irrational use (Rule 10).

TRYPARSAMIDE

Preliminary Report of the Council on Pharmacy and Chemistry

From the Journal A. M. A., May 26, 1923, p. 1521

The Council has authorized publication of the following statement on the experimental status of Tryparsamide.

W. A. PUCKNER, Secretary.

Tryparsamide is a new arsenical developed in the Rockefeller Institute for Medical Research. It is manufactured by the Powers-Weightman-Rosengarten Company for the Rockefeller Institute. Pending the outcome of clinical study, the substance is not offered for sale. At present the institute has entire control over the chemical and biologic testing and distribution of the substance.

Tryparsamide is the sodium salt of N-phenylglycineamide-*p*-arsonic acid, the formula of which is $C_6H_4(NHCH_2CONH_2)$. (As O.OH.ONa). The dried salt contains 25.32 per cent. of arsenic, in the pentavalent form. Tryparsamide is a colorless, odorless powder, readily soluble in water.

Tryparsamide is primarily a trypanocidal agent, but it possesses some spirocheticidal activity. It is said to produce "tonic" effects. It is proposed for use in the treatment of trypanosomiasis, syphilis of the central nervous system and late stages of syphilis with inactive or indolent lesions, and it is said to be especially indicated in the treatment of cachectic individuals. The use of the drug is not advised during the early stages of syphilis while lesions are actively developing. The drug can be administered subcutaneously, intramuscularly or intravenously.

The toxicity of Tryparsamide has been studied by Brown and Pearce.[1] They found the minimum lethal dose to vary

1. Brown, W. H., and Pearce, Louise: J. Exper. Med. **30**: 417 (Nov.) 1919.

between 0.75 and 2.75 gm. per kilogram of body weight for different species. The toxic effects resemble those of a number of other organic pentavalent arsenic compounds.

Trypanosome infections,[2] due to various species in different experimental animals, were very favorably influenced by doses well below those that prove toxic. Action on members of the spirochete group of organisms[3] was less pronounced. With *Spirochaeta obermeieri,* it was not possible to obtain cures in more than 75 per cent. of cases. The action on *Spirochaeta pallida* is more pronounced, but the dose required may be large. The lesions may be favorably influenced out of proportion to the action on spirochetes.

Studies have been made of the therapeutic effect of Tryparsamide in human trypanosomiasis.

Pearce[4] treated seventy-seven cases of trypanosomiasis in various stages of infection by *Trypanosoma gambiense.* It was relatively easy to sterilize the peripheral blood of patients with single doses of from 3 to 7 gm. administered intravenously, but relapses were liable to occur unless treatment was continued. Intramuscular administrations produced a longer immunity against relapse than did the intravenous administrations. The patients improved perceptibly both subjectively and objectively. The dose was repeated at intervals of one of two weeks.

Impairment of vision, occasionally permanent, occurred in a number of cases. The authors suggest that this is not necessarily due to direct toxic action of the drug but may be associated with the process of resolution of a lesion of the disease.

A report on the use of Tryparsamide in the treatment of neurosyphilis, particularly in paresis, has been furnished the Council by Lorenz, Loevenhart, Bleckwenn and Hodges.[5] The dose usually employed was 3 gm. each week. It is pointed out that there is risk of injury to the optic nerve, although in most cases the visual disturbance clears up rapidly on withdrawal or reduction of the drug. It was found desirable to carry on mercurial treatment at the same time. The authors of the report consider the results very satisfactory,

2. Brown, W. H., and Pearce, Louise: J. Exper. Med. **30**: 455 (Nov.) 1919.

3. Brown, W. H., and Pearce, Louise: J. Exper. Med. **30**: 483 (Nov.) 1919.

4. Pearce, Louise: J. Exper. Med. (Supp.) **34**: 1 (Dec.) 1921.

5. Lorenz, Loevenhart, Bleckwenn and Hodges: J. A. M. A. **80**: 1497 (May 26) 1923.

and regard them as superior to those obtainable by any other medication.

The favorable reports of the effect of Tryparsamide on trypanosomiasis and neurosyphilis appear to warrant controlled trials of the drug in these conditions. The possibility of harm to vision should be given due consideration, particularly in cases of neurosyphilis showing involvement of the optic nerve.

The Council has postponed the acceptance of Tryparsamide for New and Nonofficial Remedies until confirmatory evidence of its therapeutic value and safety is submitted, and until it is on the market and standards have been established for the control of its composition and uniformity.

INDEX OF PROPRIETARIES, MANUFACTURERS AND AGENTS